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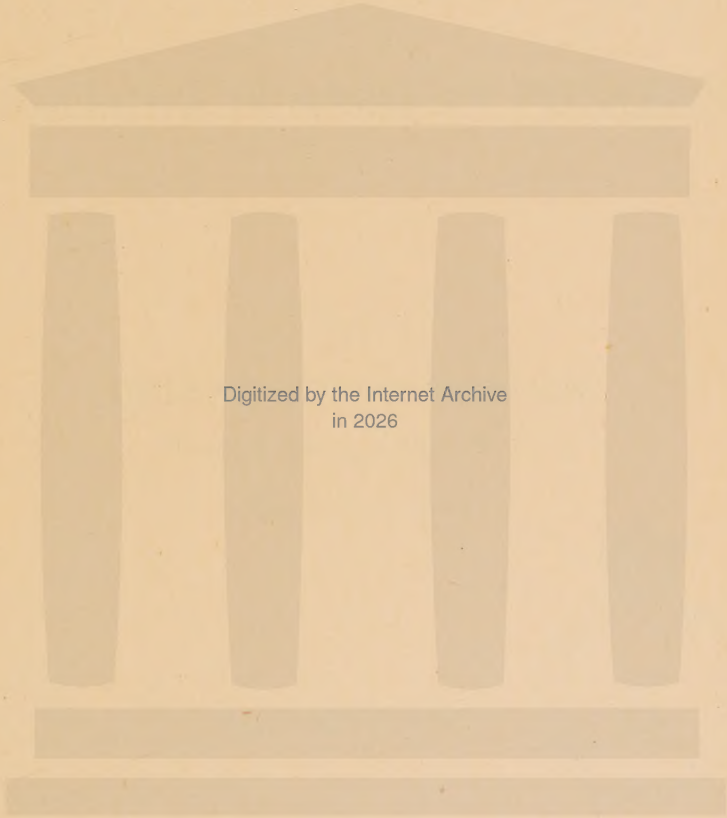
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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS

THIRTY-SECOND SESSION

HELD AT ATLANTIC CITY, N. J.

MAY 2 AND 3, 1917

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1917

NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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FROM ITS ORGANIZATION TO THE PRESENT TIME

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1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1907.	F. P. Kinnicutt.	James Tyson.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1913.	L. F. Barker.	Simon Flexner.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1914.	Simon Flexner.	S. J. Meltzer.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1915.	S. J. Meltzer.	Henry Sewall.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1916.	Henry Sewall.	George Dock.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1917.	George Dock.	F. H. Williams.	T. R. Boggs.	T. McCrae.	J. P. C. Griffith.
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1913. Anderson, John F., E. R. Squibb's Lab., New Brunswick, N. J.
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1913. Brooks, Harlow, 44 West 9th St., New York.
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1913. Bunting, C. H., University of Wisconsin, Madison.
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1917. Cohn, Alfred E., 315 Central Park West, New York.
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ELECTED

1914. Coleman, Warren, 58 West 55th St., New York.
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1908. Conner, Lewis A., 121 East 62d St., New York.
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1917. Dochez, Alphonse R., Rockefeller Institute, 66th St. and Ave. A, New York.
1893. Dock, George, 600 S. Kingshighway, St. Louis, Missouri.
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1915. Emerson, Charles P., Medical School, University of Indiana, Indianapolis.
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1900. Ewing, James, 260 West 57th St., New York.
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1908. Hamilton, W. F., 287 Mountain St., Montreal, Canada.
1915. Hamman, Louis V., 714 Park Ave., Baltimore.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1898. Herrick, James B., People's Gas Building, Chicago.
1910. Hewlett, Albion W., Stanford Med. School, San Francisco, Cal.
1911. Hoover, C. F., 702 Rose Building, Cleveland, Ohio.
1914. Howard, Campbell P., Iowa City, Iowa.
1911. Howard, W. T., 1213 N. Calvert St., Baltimore.
1911. Howland, John, Johns Hopkins Hospital, Baltimore, Md.
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1907. Hunt, Reid, Harvard Med. School, Boston.
1917. Irons, Ernest E., 122 S. Michigan Ave., Chicago.
1901. Jackson, Henry, 380 Marlborough St., Boston.
1908. Janeway, Theodore C., Johns Hopkins Hospital, Baltimore.
1916. Jobling, James W., Vanderbilt Univ., Nashville, Tenn.

ELECTED

1902. Joslin, E. P., 81 Bay State Road, Boston.
1916. Karsner, Howard T., Lakeside Hospital, Cleveland.
1901. Kinyoun, J. J., 1421 Clifton St., Washington, D. C.
1915. Klotz, Oskar, University of Pittsburgh, Pittsburgh.
1900. Koplik, Henry, 30 East 62d St., New York.
1895. Lafleur, Henri A., 251 Peel St., Montreal, Canada.
1906. Lambert, Samuel W., 130 East 35th St., New York.
1915. Landis, H. R. M., 11 S. 21st St., Philadelphia.
1917. Lee, Roger I., Harvard Medical School, Boston.
1888. Lewis, Morris J., 1316 Locust St., Philadelphia.
1910. Libman, E., 180 East 64th St., New York.
1912. Locke, Edwin A., 311 Beacon St., Boston.
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1909. Longcope, Warfield T., 41 E. 70th St., New York.
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1905. Macallum, A. B., University of Toronto, Toronto, Canada.
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1905. Meyer, Adolph, Johns Hopkins Medical School, Baltimore.
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1905. Miller, Joseph L., 122 S. Michigan Boulevard, Chicago.
1908. Moffitt, Herbert C., 240 Stockton St., San Francisco, Cal.
1915. Morris, Roger S., Cincinnati General Hospital, Cincinnati.
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1915. Noguchi, Hideyo, Rockefeller Institute, 66th St. and Ave. A, New York.
1914. Norris, Geo. W., 1530 Locust Street, Philadelphia.
1891. Northrup, W. P., 57 East 79th St., New York.
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1902. Opie, E. L., 600 S. Kingshighway, St. Louis, Missouri.
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1897. Thayer, W. S., 406 Cathedral St., Baltimore.
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1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
1912. Wilson, Louis B., 1101 W. Zumbro St., Rochester, Minn.
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1913. Duval, Charles W., Tulane University, New Orleans.
1916. Edmunds, Charles W., Univ. of Michigan, Ann Arbor, Mich.
1915. Einhorn, Max, 20 E. 63d St., New York.
1916. Eyster, John H., Univ. of Wisconsin, Madison, Wis.
1917. Hamburger, W. W., 104 S. Michigan Ave., Chicago.
1917. Hess, A. F., 16 W. 86th St., New York.
1916. Hirschfelder, Arthur D., Univ. of Minnesota, Minneapolis.
1917. Krumbhaar, E. B., Med. Dept., Univ. of Pa., Philadelphia.
1917. Lewis, P. A., Phipps Institute, Philadephia, Pa.
1916. Loevenhart, Arthur S., Univ. of Wisconsin, Madison, Wis.
1917. Meakins, J. C., 392 Mountain St., Montreal.
1917. Newburgh, L. H., Univ. Hospital, Ann Arbor.
1914. Ordway, Thomas, Albany Med. School, Albany, N. Y.
1914. Pemberton, Ralph, 2224 Locust St., Philadelphia.
1914. Plummer, H. S., Rochester, Minn.
1916. Rosenow, Edward C., Mayo Clinic, Rochester, Minn.
1917. Sellards, A. W., Harvard Med. School, Boston.
1916. Shattuck, George C., 135 Marlborough St., Boston.
1914. Smith, Elsworth, Humboldt Building, St. Louis.
1917. Warfield, L. M., 79 Wisconsin St., Milwaukee.
1916. Webb, Gerald B., Burns Bldg., Colorado Springs, Col.
1917. Weil, R., 1000 Park Ave., New York.
1915. Wolbach, S. Burt, 420 Beacon St., Boston.

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ELECTED ACTIVE MEMBER	ELECTED HONORARY MEMBER	
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*1886.	1912.	JACOBI, A., 19 East 47th St., New York.
1902.	1916.	KOBER, GEO. M., 1819 Q St., N. W., Washington.
*1886.	1912.	OSLER, WM., 13 Norham Gardens, Oxford, England.
*1886.	1913.	PRUDDEN, T. MITCHELL, 160 W. 59th St., New York.
*1886.	1915.	TYSON, JAMES, 1506 Spruce St., Philadelphia.
1889.	1915.	VAUGHAN, VICTOR C., Univ. of Michigan, Ann Arbor.
*1886.	1913.	WELCH, WILLIAM H., 807 St. Paul St., Baltimore.

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* Original Members

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
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1892.	1916.	Bolton, Meade B., Charlottesville, Va.
1898.	1917.	Brannan, John W., 48 W. 51st St., New York.
1888.	1910.	Bridge, Norman, 10 Chester Place, Los Angeles, Cal.
1889.	1916.	Cary, Charles, 340 Delaware Ave., Buffalo.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1897.	1905.	Cushny, Arthur C., University of London, London, England.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1888.	1916.	Dana, Charles L., 53 W. 53d St., New York.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A. Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, 637 S. Wood St., Chicago.
*1886.	1908.	Henry, Frederick P., 114 S. 18th St., Philadelphia
1900.	1917.	Holt, L. E., 14 W. 55th St., New York.
1890.	1902.	Hurd, H. M. Johns Hopkins Hospital, Baltimore.
1899.	1914.	James, Walter B., 17 W. 54th St., New York.
1898.	1916.	Mallory, F. B., Harvard Medical School, Boston.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1901.	1913.	Morse, John L., 70 Bay State Road, Boston.
1898.	1914.	Pfaff, Franz, Dresdner Bank, Berlin.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
*1886.	1915.	Putnam, James J., 106 Marlborough St., Boston.
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1900.	1914.	Sears, Geo. G., 19 Marlborough St., Boston, Mass.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street, Boston.
*1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
1887.	1902.	Starr, Louis, 1818 S. Rittenhouse Square, Phila.
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1889.	1917.	THOMSON, WM. H., 71 Central Park West, New York.
1889.	1904.	WALCOTT, HENRY P., 11 Waterhouse St., Cambridge, Mass.
1898.	1915.	WESBROOK, F. F., Univ. British Columbia, Vancouver, B. C.
*1886.	1911.	WILSON, JAMES C., 1509 Walnut St., Philadelphia.
*1886.	1908.	WOOD, HORATIO C, 4107 Chester Ave., Philadelphia.
1899.	1912.	WRIGHT, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

DECEASED MEMBERS

* Original Members

DATE OF ELECTION

*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Chew, Samuel C., Baltimore.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Delafield, Francis A., New York.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
1895. Fischel, William E., St. Louis.
*1886. Fitz, Reginald H., Boston.
*1886. Folsom, Chas. F., Boston.
*1886. Forchheimer, F., Cincinnati.
*1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Atken, S. C.
*1886. Graham, J. E., Toronto, Canada.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, Jr., E. Darwin, New York.
*1886. Hutchinson, James H., Philadelphia.
*1886. Janeway, E. G., New York.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.

DATE OF ELECTION

*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.
*1886. Kinnicutt, Francis P., New York.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Longstreth, Morris, Cambridge, Mass.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
1890. MacDonnell, R. P., Montreal, Canada.
*1886. McBride, Thomas A., New York.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Springs, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
1898. Mitchell, John K., Philadelphia.
*1886. Mitchell, S. Weir, Philadelphia.
1887. Musser, John H., Philadelphia.
1898. Packard, Frederick A., Philadelphia.
*1886. Peabody, George L., Newport, R. I.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
1893. Rotch, Thomas M., Boston.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
*1886. Smith, A. A., New York.
1891. Smith, Andrew H., New York.
1905. Steele, J. Dutton, Philadelphia.
*1886. Sternberg, Geo. M., Washington.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
*1886. Trudeau, Edward L., Saranac Lake.
*1886. Ward, Samuel B., Albany.
*1886. Whittaker, James T., Cincinnati.
*1886. Wilkins, George, Montreal.
1898. Withington, Charles F., Boston.

ASSOCIATION

OF

AMERICAN PHYSICIANS

CONSTITUTION

As Amended May 10, 1916

ARTICLE I

OBJECT AND NAME

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

ARTICLE II

MEMBERS

The number of active members shall be limited to one hundred and sixty. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Provided, That in case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered, should it so desire, to transfer the name of such a member during his absence to the list of emeritus members, without regard to the length of his previous active membership.

ARTICLE III

OFFICERS

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

ARTICLE IV

DUTY OF OFFICERS

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of TRANSACTIONS.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

ARTICLE V

COUNCIL

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the

Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

ARTICLE VI

MEETINGS

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the TRANSACTIONS as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII

QUORUM

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution twenty-five members shall be necessary.

ARTICLE VIII

ELECTION OF MEMBERS

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the

nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The elections of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX

ANNUAL DUES

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

ARTICLE X

AMENDMENTS TO THE CONSTITUTION

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

THIRTY-SECOND ANNUAL MEETING

Held at the Hotel Traymore, Atlantic City, N. J., May 2, 3 and 4, 1917

The following members were present at the meeting:

Abel, John J.
Allen, Frederick M.
Barker, L. F.
Blumer, George
Boggs, Thomas R.
Brill, Nathan E.
Brown, Lawrason
Brown, Philip K.
Capps, Joseph A.
Christian, Henry A.
Cohen, Solomon Solis
Cohn, Alfred E.
Cole, Rufus I.
Coplin, W. M. L.
Dochez, Alphonse R.
Dock, George
Edsall, David L.
Einhorn, Max
Emerson, Charles P.
Flexner, Simon
Ford, W. W.
Foster, Nellis B.
Freeman, R. G.
Friedenwald, Julius
Frothingham, C., Jr.
Fussell, M. Howard
Futcher, Thomas B.
Greene, Charles L.
Griffith, J. P. Crozer
Hamilton, W. F.
Hamman, Louis V.
Hare, Hobart A.
Herrick, James B.
Hoover, C. F.
Howard, Campbell P.
Howland, John
Hunt, J. Ramsay
Irons, Ernest E.
Jacobi, A.
Janeway, Theo. C.
Joslin, E. P.
Kinyoun, J. J.
Klotz, Oskar
Kober, George M.
Koplik, Henry
Landis, H. R. M.
Libman, E.
Locke, Edwin A.
Longcope, W. T.
Lord, Frederick T.
McCrae, Thomas
McPhedran, A.
Macallum, A. B.
Martin, Charles F.
Meltzer, S. J.
Miller, James A.
Miller, Joseph L.
Mosenthal, Herman O.
Northrup, W. P.
Peabody, Francis W.
Pemberton, Ralph
Pratt, Joseph H.
Prince, Morton
Riesman, David
Robinson, G. Canby
Rowntree, Leonard G.
Sailer, Joseph
Smith, Elsworth
Sollmann, Torald H.
Southard, Elmer E.
Steiner, Walter R.
Stengel, Alfred
Stockton, Charles G.
Thayer, W. S.
Webb, Gerald B.
Welch, William H.
White, Franklin W.
White, Wm. Charles
Williams, Francis H.
Wilson, Louis B.
Woodyatt, Rollin T.

Wednesday, May 2

Morning Session.—The Association was called to order by President Dock, at 10 A.M., who then delivered the President's address.

The Treasurer presented his report, showing receipts to have been $2336.49; expenditures, $1891.17, leaving a balance of $445.31. The report was referred to an auditing committee composed of Dr. J. Friedenwald and Dr. O. Klotz.

The Secretary presented the following recommendations from the Council:

That the dues for this year be $15 for practitioners, $7.50 for associate members, and $5 for laboratory workers, and that the *Transactions* be $4 a volume.

The list of nominations, as given elsewhere, for officers and new members.

The following amendments to the Constitution were proposed:

Article II, Members: In Paragraph I, change the words "one hundred and sixty" to "two hundred and fifty."

Omit paragraph 3 relating to Associate Members.

Add a new paragraph. "Membership shall also be forfeited unless some meritorious contribution to medicine is published at least once in three years."

Article VII, Quorum. Change the words "fifteen" to "twenty-five" and "twenty-five" to "fifty."

Francis H. Williams,
A. McPhedran,
W. S. Thayer,
Theodore C. Janeway,
Thomas R. Boggs.

In view of the long services of Dr. Griffith as Treasurer, on motion of Dr. Janeway, seconded by Dr. Williams, a vote of thanks and appreciation was tendered to him.

Dr. Dock presented the report of the Committee (Drs. Conner, Christian, and Kinyoun) on the matter of National Defense. This was adopted.

The programme was then proceeded with.

Dr. F. W. White presented a paper on "Studies of Digestion: (*a*) Control of Pylorus by Reflexes from Lower Bowel. (*b*) Effect of Massage on the Colon," which was discussed by Dr. Meltzer and the discussion closed by Dr. White.

Dr. M. Einhorn presented a paper on "The Importance of Duodenal Alimentation in Severe Dyspepsia Occurring after Gastro-enterostomy," which was discussed by Drs. Friendenwald, Stockton, and F. W. White.

Drs. W. W. Ford, K. D. Blackfan, and M. D. Batchelor presented a paper on "Some Observations upon Intestinal Bacteria in Children," which was discussed by Dr. William H. Welch.

Dr. H. Z. Giffin presented a paper on "Observations on Treatment of Myelocytic Leukemia by Radium," which was discussed by Drs. Stengel, Peabody, Foster, Rowntree, Barker, Libman, Mosenthal, Thayer, Cohen, Capps, and the discussion closed by Dr. Giffin.

Dr. C. F. Hoover presented a paper on "The Mechanism of Lung Ventilation," which was discussed by Drs. Meltzer and Jacobi, and the discussion closed by Dr. Hoover.

Dr. R. G. Pearce presented a paper on "Cyanosis of Pneumonia," which was discussed by Drs. Hoover and Meltzer.

Dr. A. Stengel presented a paper on "Clinical and Pathological Features of Bronchiectasis," which was discussed by Drs. Lord, E. Smith, Meltzer, Cohen, and the discussion closed by Dr. Stengel.

Wednesday, May 2

Afternoon Session.—Drs. J. Friedenwald and J. M. T. Finney presented a paper on "Gastric Polyposis," which was discussed by Drs. Thayer and Janeway, and the discussion closed by Dr. Friedenwald.

Dr. L. Hamman and I. Hirschman presented a paper on "Alimentary Hyperglycemia following the Repeated Ingestion of Glucose;" and Drs. S. J. Meltzer and I. S. Kleiner presented a paper on "The Cause of the Glycosuric (and Hyperglycemic) Effect of Painting the Pancreas with Adrenalin (Herter)." These papers were discussed by Drs. Mosenthal, Woodyatt, and Allen.

The "Symposium on Diabetes" was presented as follows: "The Present Outlook of Diabetic Treatment," by Dr. F. M. Allen; "The Maintenance Diet in Diabetes Mellitus," by Dr. H. O. Mosenthal; "Diabetes in Children," by Drs. E. P. Joslin and H. Gray; "The Association between Diabetes Mellitus and Tuberculosis," by Dr. S. Solis Cohen; and "Acetone Bodies in the Blood in Diabetes," by Dr. R. Fitz. The discussion was opened by Dr. N. B. Foster and participated in by Drs. Van Slyke, Meltzer, Jacobi, Allen, Joslin, and Cohen.

Evening Session.—Dr. J. A. Miller presented a paper on "Subacute and Chronic Non-tuberculous Pulmonary Infections," which was discussed by Drs. Herrick, Brill, Webb, Hare, Cohen, Lawrason Brown, and the discussion closed by Dr. Miller.

Drs. H. R. M. Landis, H. K. Pancoast, and T. G. Miller presented a paper on "A Röntgenologic Study of Pneumoconiosis," which was discussed by Drs. Kober, Coplin, Stockton, Edsall, and the discussion closed by Dr. Landis.

Drs. E. E. Smith and H. G. Mudd presented a "Report of a Case of Bronchiectasis Treated Successfully by a New Surgical Method," which was not discussed.

Drs. G. W. Norris and G. Fetterolf presented a paper on "Frozen Sections from a Case of Sternum-eroding Aortic Aneurysm," and Dr. H. A. Hare presented a paper on "Cases of Aortic Aneurysm Treated by Wiring," which were discussed by Drs. Sailer, Coplin, and Northrup.

Drs. C. Lundsgaard and D. D. Van Slyke presented a paper on "Studies on Lung Volume," which was not discussed.

Dr. Joseph Sailer presented a paper on "A Case of Adams-Stokes' Disease," which was discussed by Drs. Wilson, McPhedran, and Cohn.

Dr. C. L. Greene presented a paper on "The Drop Heart Considered as a Source of Serious Diagnostic Error."

Dr. G. C. Robinson presented a paper on "A Case of Ventricular Fibrillation, with Recovery," which was discussed by Dr. Rowntree.

Dr. M. A. Blankenhorn presented a paper on "The Occurrence of Bilirubin in the Plasma and other Body Fluids," which was discussed by Dr. Meltzer and the discussion closed by Dr. Blankenhorn.

Dr. D. Riesman presented a paper on "Cases Illustrating the Causation and Curability of Certain Long-standing Albuminurias," which was discussed by Drs. Janeway, Meltzer, Christian, Thayer, Rowntree, and Fussell.

Drs. J. H. Pratt and C. W. McClure presented a paper "On the Elimination of Uric Acid in Gout and Other Forms of Arthritis," which was discussed by Drs. Christian, Barker, Jacobi, and the discussion closed by Dr. Pratt.

Drs. J. Howland and Wm. McK. Marriott presented a paper on "A Consideration of Calcium and Magnesium in the Blood in Rickets and Tetany," which was discussed by Drs. Rowntree, Koplik, Meltzer, Wilson, and the discussion closed by Dr. Howland.

Drs. L. F. Barker and H. O. Mosenthal presented a paper on "The Influence of Pituitrin upon the Urinary Excretion in Diabetes Insipidus," which was discussed by Drs. J. L. Miller, Futcher, Meltzer, S. S. Cohen, Koplik, McPhedran, and the discussion closed by Drs. Barker and Mosenthal.

Drs. C. P. Howard and C. E. Royce presented a paper on the "Report of a Case of 'Wilson's Disease' with Postmortem Findings," which was discussed by Drs. Klotz, Meltzer, Hunt, Rowntree, Barker, Kober, and the discussion was closed by Dr. Howard.

Dr. H. A. Christian presented a paper on "The Nervous Symptoms of Polycythemia Vera," which was discussed by Drs. Thayer and Sailer, and the discussion closed by Dr. Christian.

Dr. H. Koplik presented a paper on "Tachycardia in Childhood."

The Association then went into Executive Session. The following Officers, Active Members, and Associate Members were elected.

President—Francis H. Williams.

Vice-President—Alexander McPhedran.

Secretary—Thomas McCrae.

Recorder—Thomas R. Boggs.

Treasurer—Joseph A. Capps.

Councillor—Theodore C. Janeway.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons—Richard P. Strong.

Alternate Representative—Francis W. Peabody.

Active Members—A. E. Cohn, New York; A. R. Dochez, New York; C. Frothingham, Boston; E. E. Irons, Chicago; R. I. Lee, Boston; J. A. Miller, New York; H. O. Mosenthal, Baltimore; H .F. Swift, New York; F. W. White, Boston; E. J. Wood, Wilmington, N. C.

Associate Members—T. Addis, San Francisco; J. H. Austin, Philadelphia; W. W. Hamburger, Chicago; A. F. Hess, New York; E. B. Krumbhaar, Philadelphia; P. A. Lewis, Philadelphia; J. C. Meakins, Montreal; L. H. Newburgh, Ann Arbor; A. W. Sellards, Boston; L. M. Warfield, Milwaukee; R. Weil, New York.

The Auditors reported that the Treasurer's accounts had been audited and found correct.

Thursday Afternoon, May 3

Dr. J. L. Miller presented a paper on "The Use of Foreign Protein," which was discussed by Drs. Irons, Cohen, Herrick, Fussell, and the discussion closed by Dr. Miller.

Dr. C. Frothingham, Jr., presented a paper on "Renal Function during Acute Infections," which was discussed by Drs. Janeway, Christian, and Rowntree.

Drs. A. R. Dochez and O. T. Avery presented a paper on "Studies on a Soluble Substance of Bacterial Origin Produced by Pneumococcus," which was discussed by Dr. Cole.

Dr. O. Klotz presented a paper on "Some Points Respecting the Localization of Syphilis of the Aorta."

Dr. N. E. Brill presented a paper on "A Case of Primary Thrombophlebitis of the Hepatic Vein; a Case of Primary Sarcoma of the Epicardium," which was discussed by Dr. Christian, and the discussion closed by Dr. Brill.

Thursday Evening, May 3

Dr. R. Cole presented a paper on "Specific Treatment of Pneumonia;" and Drs. H. A. Christian and H. L. Alexander one on "Observations at the Peter Bent Brigham Hospital on Cases of Pneumonia in Relation to Types of Pneumococci and the Serum Treatment of Type I Cases," which was discussed by Drs. Janeway, Fussell, Meltzer, and the discussion closed by Dr. Cole.

Dr. L. B. Wilson read a paper on "Experimental Lesions in the Cervical Sympathetic Ganglia" which was discussed by Dr. Meltzer, and the discussion closed by Dr. Wilson.

Drs. R. E. Morris and L. G. Rowntree presented a communication on "Graphic Records of Reflexes, Clonus and Tremors."

Dr. J. R. Hunt read a paper on "The Relation of the Globus Pallidus Mechanism to Paralysis Agitans."

Dr. E. E. Southard presented a paper "On the Focality of Microscopic Lesions in the Brains of Certain Psychopathic Subjects, especially in Dementia Precox."

Drs. H. T. Karsner and S. P. Reimann presented a communication on "Studies on Uranium Poisoning."

1. Toxic Effects of Certain Aqueous Insoluble Salts of Uranium.
2. Solubility of Uranium Oxide in Artificial and Human Gastric Juice.
3. Effects of Soluble Uranium Salts on Blood, Blood Plasma, and Erythrocytes.
4. Localization on Uranium in Body Tissues.
5. Hydrogen-ion Concentration of the Blood in Uranium Poisoning.

The paper of Dr. I. Adler on "Further Studies in Experimental Atherosclerosis" was read by title.

On motion of Dr. Meltzer, seconded by Dr. Thayer, a vote of thanks was given to Dr. Dock for the interesting programme and for the able administration of his office.

Thomas McCrae, M.D.,
Secretary.

ADDRESS OF THE PRESIDENT

By GEORGE DOCK, M.D.
ST. LOUIS, MISSOURI

The position I hold through your grace exacts an address. Like many of my predecessors I shall make mine brief, and like several of them I shall speak chiefly of the internal policy of the Association.

Death has not spared us in the past year. Of three taken, one, George Wilkins, of Montreal, was an original member and became Emeritus in 1911.

Charles F. Withington, of Boston, became a member in 1898.

John Kearsley Mitchell, the most recent loss, was elected in the same year. With his passing goes one of our links with the early days of American Medicine and one of the most notable American medical families. His keen mind, devoted almost wholly to the practice of medicine, showed the same qualities that were so brilliantly exercised by his father, S. Weir Mitchell, and his grandfather, for whom he was named. The three generations covered just a century of time in medicine and left a record difficult to equal for brilliant and prophetic speculation, painstaking and accurate investigation, and sound, well-directed medical practice.

The thirty-second annual meeting finds our Association, and finds the world, in a situation that emphasizes the need and importance of such an organization. This Association was founded in a time of profound political peace, but of increasingly rapid change in biological science, and founded "for the advancement of scientific and practical medicine." At the very beginning it was felt that it was not enough to accept the gifts of discovery and invention, rich as those gifts had proved to be. The necessity for more active research, for the greatest efficiency, for coördination and coöpera-

tion in the medical profession were all clearly recognized. The movement, I am sure, has helped all of us through a period of national extravagance and waste in all lines of human activity. With the need of not only greater, but the greatest, efficiency that now faces the nation, the briefly worded statement of our founders is a trustworthy guide, and whether we work as an organization or as individuals we cannot fail if we follow it to the best of our ability.

Many before me on similar occasions have spoken of the size of our membership, and with 50 candidates for active membership and about one-fifth as many vacancies it seems to me time to renew the discussion.

Beginning with a membership limited to 100 and an actual membership of 70, we have now, in thirty-one years, reached a total membership of 215. There are 147 Active, 25 Associate, 34 Emeritus, and 9 Honorary Members. The intention from the beginning was to make membership select, to make it the highest goal of those who devote themselves to the progressive, the investigative, the scientific side of medicine. The original members reflected well the possibilities of the times. Nearly all who were eligible were engaged in the practice of medicine, not a few as general practitioners. Even in the non-clinical branches of medical teaching, which furnished some members, this was almost equally true. Opportunities for a scientific career at that time were few and their financial returns indicated plainly that they were not for those who had given hostages to fortune. Those who became eligible did so often by reason of long-continued devotion in the face of many difficulties. Advancement for young men was slow and precarious. Many who began with great promise were driven by force of circumstances into work that, however valuable and meritorious, precluded intense cultivation of the scientific side. Since that time, less than a third of a century ago, the population of the United States has nearly doubled, while that of Canada, though it has not increased in proportion, promises rapidly to gain. Not less striking have been the changes in the methods of medical teaching and study and in the opportunities for research and for careers other than in the practice of medicine. With 50 per cent. more schools there are far more

positions that offer means of continued scientific work in general; there are far better facilities for the labors and consequently the advancement of young men, and more certainty of being able to continue the scientific career through life. There are many new subdivisions of medical work within our own specialty, and these offer, even more than strictly medical lines, not only academic positions, but many equally congenial places in governmental and other services in which phases of scientific medicine can be pursued. From these facts, which have become established in little more than half the lifetime of the Association, a considerable increase of membership might reasonably be expected, even if we interpreted most strictly the criterion so well expressed by Dr. Osler in his presidential address—"Has the man done good work?" Yet whenever the proposal to enlarge the membership has been made, and it has been made by some of the most illustrious Presidents from about five years after the beginning, opposition and delay have occurred or the proposal has been voted down. More than once the belief has been expressed that small size has some special virtue. This seems to me a wrong view. While there is something awe-inspiring in a small but illustrious body like the Académie française, there is no mechanism or tradition by which such a limitation could acquire adequate prestige in the new world. The honor lies not in the limitation but in the selection. A larger body, provided the basis of selection is well founded and safeguarded, can be just as select and the pride taken in membership equally great if not greater.

The specialty of medicine, though a broad one and highly subdivided, is still easily circumscribed. By containing the largest possible number of members of the requisite standing the influence of the body would be greater rather than less. As Dr. Adami well said, "It is healthy and broadening for the young physician to know that work well done will obtain recognition—by a body—above and beyond local and even national considerations." Since this is the body that can best have such a stimulating effect, and as the stimulus will be most desirable for the benefit of medicine itself, a liberal use of the recognition can have only good results. The Association was not intended to be, and can hardly become, a body

of laureates content with their honors. Therefore it should gain if all who demonstrate special interest in and capacity for advancing internal medicine and who show promise of continuing to do so could be admitted. To me it is beyond question that if we could receive all who reach our standards soon after the capacity of the aspirant is demonstrated there would be a most desirable stimulation, and corresponding elevation, of scientific medical spirit.

Here some may object that with a great increase of membership the annual program would become unwieldy. This is an unnecessary fear, because a very large immediate increase can hardly be expected. Moreover, we have become much more skilful in presenting contributions than we were in earlier days, and we can do still better in future.

Let me consider some of the details of membership.

Associate membership was one of the methods of enlarging the size of the body without affecting the formal membership. It has been of great service in bringing to our meetings men of ability who were not able to enter the crowded list of Active Members. Perhaps in the beginning it was useful to have such a body as probationers, but it is no longer so, and there are other organizations in which novices can show their capacity and from which promising material can be selected. The plan once considered, of taking all Active Members from this other rank, proved to be impracticable. As much care is properly devoted to the selection of Associates as of Active Members. If Associates become unable to meet the second test within the prescribed time and are dropped, they probably reflect as much on the judgment of this body as on their own capacity. Such a possibility shows the need of greater expansibility of active membership.

The Emeritus division was adopted in 1909, after using the Honorary membership for four years for the same purpose, *i. e.*, retiring Active Members. Even as early as 1897 that sort of accelerated retiring was advocated as a means of enlarging membership. Taking Emeritus rank is a rational and natural way to retire those who are no longer able to attend frequently or to take an active part in meetings, and it should be separated, as it is now, from the Honorary list. When it is advocated as a means of hastening

retiring of Active Members for the admission of new members it shows an essential fallacy. Perhaps this is best illustrated by the fact that it has been suggested that members might take emeritus rank after ten years, or as otherwise expressed, at from forty-five to fifty years of age. Of those who have accepted emeritus rank many have done so after twenty-five or more years of active membership. Some of these were the most productive members up to the time of retiring, while two of those who retired early, after thirteen years in each case, belong to the number most valued at annual meetings. Their interest should have been stimulated rather than discouraged. It has been too much the custom for American physicians to retire from active participation in the work of advancing science at an earlier age than happens in other countries, and at an age when in other walks of life men are often active and useful. Even if no longer doing the same sort of work they did before, at meetings or otherwise, such men should be of value as critics and guides, and if, as has happened, they sometimes give an example of how not to do things, this should be useful to younger members as a warning.

There is another reason for a broad membership. As medical schools grow in size of teaching force it becomes increasingly important, as it is increasingly difficult, to maintain high qualifications in teachers. Membership in exclusive societies should be required in making academic appointments. It should not be too much to insist that appointments of the rank of associate professor or assistant professor or above should not be made except to members of such societies. But in order to stimulate this practice there should be no accidental bar, such as lack of room, that might delay or prevent the election of a man who had proper qualifications.

Let me consider some of the objections to an increase in size. It has been said that with large—that is unlimited—membership the Association would become a rival of the American Medical Association. Of course the comparision should rather be with a few sections of that body, with the great difference that the national organization is very properly open to all, while our members must be selected on specific grounds. But no matter how large, this Association would not need to take over any of the functions of the

American Medical Association except the technical ones now lodged in the sections. We do not need to discuss medical economics or politics. They have their value and their time and place, and the latter are well provided for by the American Medical Association, and although we have at least once put ourselves on record in a non-technical matter, our chief interest must always be scientific or technical.

A better example can be found abroad. I, and doubtless many others, here, have admired in more peaceful times the work of the German Kongress f. innere Medicin. It was begun four years before our Association. It has a population a little less than ours to draw from, if one can compare the single linguistic, chiefly racial group there and the miscellaneous population in our country. With fewer medical schools in the Teutonic countries there are many more great hospitals with expert staffs fitted for and contributing to medical advance. In 1914, before the war, the membership was 706 and the attendance 737. There they have the practical method of permitting participation on payment of a fee equal to the annual dues.

Of course we cannot count on such a body now, but unless we carry on our training to at least the same intensity within the next decade or two we cannot expect to hold the rank in medicine equivalent to our expected rank in population, wealth, and political power. There is a small detail connected with large membership that one hesitates to mention in these expansive days when wealth is so ruthlessly dissipated. The annual dues in the Kongress f. innere Medicin are as many marks as ours are dollars, or one-fourth as much.

In making a suggestion on this subject I realize that I have no power *ex officio*. I would, however, offer the suggestion that a line of advance would consist in ending the Associate Membership by taking on no new members and by dropping it when all now in the list are either active or no longer eligible; next, by withdrawing the pressure on Active Members to become Emeritus; finally, by raising the present limit of membership and retaining the standard of admission. An important detail with larger membership would be a more active search for and recommendation of candidates.

I am sure some of us in the past have hesitated to nominate promising men because of the slight chance of final election.

Let me touch briefly on another subject—consideration of non-technical questions. We have been singularly consistent in our annual programs in adhering to topics closely related to our specific work as physicians and investigators. As I have intimated, there is no need for our participation in many of the questions that properly come before the American Medical Association. But can we remain always aloof from certain great social questions as we have in the past? With the upheaval of standards and methods in all lines of human activity, with the exciting of passions and the loss of calmness that accompany all great political disturbances, will there not be a demand for the exact training, the cool consideration, the power of impersonal and dispassionate judgment that such a body as ours represents? Can we refuse, either as individuals or as a body, to act or to go on record when we see or hear a call for assistance? I think not. Very recently such a call came, and at the proper time you will have an opportunity of considering the action of your President and that of a committee he appointed. I hardly think it necessary to take action of a general kind covering such activity in future, but beg to leave the thought for future consideration.

THE IMPORTANCE OF DUODENAL ALIMENTATION IN SEVERE DYSPEPSIA OCCURRING AFTER GASTRO-ENTEROSTOMY

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Gastro-enterostomy is the most frequent operation performed in organic disease of the stomach and duodenum. Not rarely after the operation the patient manifests a new train of symptoms which sometimes are just as severe—if not severer—than those existing before the operation. Peptic ulcers in the stomach or jejunum in the vicinity of the new stoma, or adhesions, are the most frequent conditions causing the new disturbances. The most prominent symptoms encountered are pains, vomiting, and hemorrhages. Usually it is possible by a thorough examination and careful handling of the situation to ameliorate the symptoms. Liquid diet, large doses of bismuth, and washing the stomach play an important part. Occasionally, however, all these measures fail and we are then at a loss to know what to do. Many of these patients have to undergo another operation, frequently with an indefinite result as to the future.

It is in this class of cases that we have frequently found duodenal (or, more correctly, jejunal) alimentation to be of great benefit, and I therefore consider it of interest to discuss this subject.

Whenever we have to deal with postoperative dyspeptic symptoms of a graver nature, it is best to make a thorough analysis of the case with regard to gastric secretion and food retention. Examination with the duodenal bucket is here of great importance. The string attached to the bucket shows whether there is a patent

opening leading into the duodenum or jejunum; whether there be ulceration at the stoma, and ultimately whether the bucket has passed through the pylorus or through the new opening. The presence of a blood stain on the string below eighteen or nineteen inches speaks for ulceration near the stoma. If a yellow coloration (bile) appears on the string, beginning at about twenty-three inches or farther down, it usually indicates that the bucket has passed through the pylorus. If the yellow discoloration begins at nineteen or twenty inches, it indicates that the bucket has passed through the new opening—for the distance from the cardia to the new stoma is much less than to the pylorus. Should there be a yellow discoloration on the string up at sixteen or seventeen inches, then we remain in the dark as to the patency of either the pylorus or the new stoma. We only know that there is a regurgitation of the intestinal contents with bile into the stomach, but we are in doubt as to how far the bucket has gone. In order to clear up this point, *x*-ray examinations with bismuth will be required.

In all cases in which the duodenal bucket has reached either the duodenum or the jejunum, treatment by duodenal or jejunal alimentation may be tried. This procedure gives complete rest to the stomach and pylorus, or the new opening, respectively, and so serves to ameliorate the condition.

Within the last few years I have had a considerable number of postoperative cases of severe dyspepsia treated by this method. I have kept track of ten of them. Two of these will be described briefly in detail; the others will be presented in table form for the sake of conciseness.

Case I.—C. H. C., a physician, aged fifty-six years, was admitted to the German Hospital February 28, 1917. September 28, 1914, he was injured in a trolley accident, suffering a fracture of the scapula and contusions of the entire body. Bleeding was profuse from an injury to the ulnar artery of the left arm. He was taken to the hospital where he remained for nine weeks. During the first three weeks he vomited continuously, and at the same time had a sharp pain in the left epigastrium. On breathing he had a sharp pain in the upper left chest. On the third day after the accident he vomited some bright red blood. He was very nervous, requiring bromides. The left arm was bandaged for eight weeks after

the accident, and after the bandage was removed he suffered severely from "rheumatism." The stomach then began to give him much trouble, and he suffered from severe eructation of gas and sour fluid; this so irritated the throat that he required gargles.

In the last week of April, 1915, he contracted a severe cold and coughed and expectorated much red blood. In the following June the pain in the region of the stomach became much worse. In July he weighed 198 pounds. About this time he ordered a suit of clothes, the trousers waist measure being 38 inches, for delivery in four weeks, and then found that his waist measured 42 inches. The patient thought that this was due to his stomach being dilated. The pain and soreness in the stomach region grew much worse, and he began to lose flesh. He went to California for a change of climate, but still grew worse.

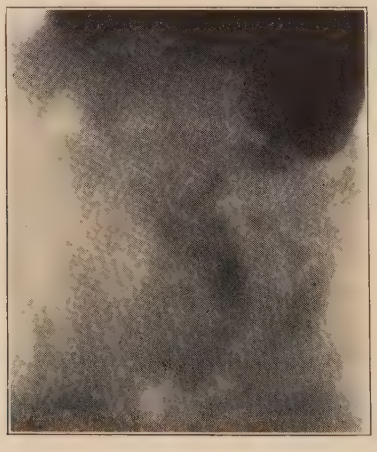

FIG. 1.—X-ray photograph of C. H. C.'s stomach after the ingestion of a bismuth-milk mixture. The gastro-enterostomy opening is distinctly visible.

After Christmas he came to New York and entered the German Hospital for observation for a week. At this time he weighed 173 pounds.

January 26 a gastro-enterostomy was performed. The patient had a severe time from hiccoughs and vomiting for a week after the operation, after which he went on to recovery. The pains, etc., were relieved, but he still had a burning feeling after drinking hot or irritating fluids.

February 19, 1917, he ate a heavy meal of fish that did not taste fresh, and had an attack of acute indigestion. His stomach became distended and he had sour eructations. That night he had a hemorrhage from the stomach, with bloody stools, and a little later he fainted, appar-

ently from loss of blood. He suffered from nausea, dizziness, thirst, restlessness, etc. After coming back to consciousness, he vomited almost a quart of bloody fluid. He remained in the hospital for ten days and went on to recovery.

February 28 he entered the German Hospital on account of gastric pains and extreme weakness. The stomach in the fasting condition showed food retention from the day before. The duodenal bucket test revealed a bile stain from 85 to 100 cm. and no blood stain. The diagnosis of gastric ulcer was made and patient was given duodenal feeding. The *x*-ray showed that the food passed through the new stoma (Fig. 1). The duodenal tube, likewise, can be seen running through the gastro-enterostomy,[1] the capsule

FIG. 2.—X-ray of C. H. C.'s abdomen, after filling the duodenal tube with a bismuth mixture. The tube is visible in the small intestine.

lying in the jejunum (Fig. 2). Weight 182½ pounds. He lost a little at first, but at the end of a two weeks' course of jejunal feeding he weighed 187½ pounds. Patient was discharged on March 19, feeling very well.

CASE II.—R. K., a cook, aged thirty-six years, was admitted to the German Hospital November 14, 1910, suffering from epigastric and right upper abdominal pains, coming on one to three hours p. c.; vomiting every three or four days, not bloody; loss of weight, thirty pounds; bowels constipated; felt weak. His family and past history were negative.

While in the hospital his urine examination was negative; his temperature was normal; pulse 100. His bowels moved with the aid of enemas.

[1] I am indebted to Dr. William H. Stewart for the five *x*-ray photographs (Figs. 1 to 5) made for me.

Stomach examination: A. C., HCl, 52; total acidity, 60; blood +. P. C., HCl, 50; total acidity, 75; blood, 0. Discharged December 4, 1910, cured, as result of diet (eggs, milk, etc.).

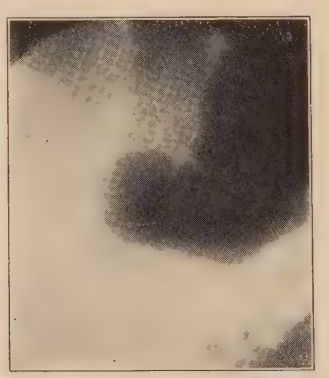

FIG. 3.—X-ray of R. K.'s stomach after ingestion of bismuth. The new stoma is entirely closed and the bismuth passes through the pylorus.

FIG. 4.—Same as Fig. 3, with the duodenal tube in the digestive tract. The capsule end of the tube can be seen lying in the small intestine to the right of the spine.

October 30, 1916, he again entered the hospital. Had been well for a year and a half after leaving the hospital, but soon began to eat and drink indiscriminatingly, and his attacks returned. On entering the hospital he was weak and had a distended and tympanitic abdomen. He was operated on by Dr. H. Fischer for a perforated duodenal ulcer. The perforation was closed and a gastro-enterostomy was performed with the Murphy button,

which was successfully passed. The urine showed a trace of albumin. He was discharged as cured November 17, 1916.

February 15, 1917, he reëntered the hospital, complaining of pain in the midabdomen. His temperature was normal. Patient had pains in the gastric region almost constantly and vomited frequently. Blood-pressure = 105-85. String test showed no blood and bile below twenty-four inches indicating that the bucket had passed through the pylorus. There was some epigastric tenderness. Urine was negative.

X-ray showed closed stoma and food passing through pylorus. (See Figs. 3 to 5.) Gastric analysis: A. C., free, 20; total, 32; no blood. P. C., free, 38; no blood, total, 54.

Fig. 5.—Same as Fig. 4. The duodenal tube filled with a bismuth mixture. The tube is visible and runs through the stomach and pylorus and reaches the jejunum.

March 5, 1917: D. C., greenish, alk., 5; A, 4 mm., erythrodextrin; T, 1 mm.

March 6. D. C., greenish-yellow, alk., 10; A, 6 mm.; S, 3 mm.; T, 3 mm.

March 2. Retention meal, few granules of rice; no raisins. Stool, faint trace of blood (guaiac).

February 29. Urine—Reaction, acid, sp. gr., 1022; color, yellow; albumin, negative; sugar, negative; microscope, leukocytes, and epithelium.

Patient was then given duodenal alimentation. As soon as the tube reached the duodenum and feeding was commenced he felt free from pain and remained so. A week after the duodenal alimentation, which had been kept up for two weeks, patient gained five pounds.

TABLE OF CASES OF SEVERE POST-OPERATIVE DYSPEPSIA TREATED WITH DUODENAL OR JEJUNAL ALIMENTATION.

Name.	Nature of operation.	Principal symptoms.	Gastric contents.	Duodenal bucket.		Remarks.
				Blood stain.	Bile stain.	
1. Elwood H. .	Gastro-enterostomy, May, 1914	Severe epigastric pains	HCl+; acidity = 75; blood +	19½″ to 20½″	26½″ to 31½″	
2. Miss Marie H.	(1) Gastro-enterostomy (2) Pyloric occlusion, April, 1915	Gastralgia and vomiting	HCl+ trace; acidity = 30	15″ to 16″	26½″ to 40″	Pylorus patent: duodenal bucket confirmed by *x*-ray examination.
3. Mrs. H. K. .	Gastro-enterostomy and pyloric occlusion, February, 1915	Distress after eating, and frequent vomiting	HCl+; acidity = 55	19″ to 20″	20½″ to 32″	Pylorus patent: duodenal bucket confirmed by *x*-ray examination.
4. Solomon S. .	Gall-bladder operation, February, 1915	Pains late after meals, also hunger pains	HCl+; acidity = 100	20½″ to 22½″	26″ to 29″	
5. Thomas K. .	Gastro-enterostomy, March, 1916, for perforated duodenal ulcer	Epigastric pain; constant vomiting	HCl+; acidity = 80; slight food retention	21″	24″+	Duodenal bucket passed through pylorus; duodenal alimentation for 2 weeks; during this period perfect euphoria; when feeding by mouth was resumed, pains returned; *x*-ray showed tube lying in pylorus and duodenum, no bismuth going through gastro-enterostomy
	Operation No. 2, anterior gastro-enterostomy	.....	....	.....	.....	Second operation: anterior gastro-enterostomy.
6. Mrs. Sadie S. .	Operation, 1913: gastro-enterostomy	Repeated hemorrhages and gastric distress	HCl+; acidity = 50; occult blood +	19″ to 20″	20″+	Duodenal bucket went through gastro-enterostomy; ulcer in stomach; *x*-ray diagnosis: carcinoma. Duodenal alimentation brought benefit for six months, then a new hemorrhage, and again duodenal alimentation was utilized.
7. Archibald S. .	1914, gastro-enterostomy	Severe pains late after eating, and hunger pains	HCl+; acidity = 60	19″	20″	In 1914 operated for gastric ulcer; gastro-enterostomy; three months later HCl+, acidity 60; blood stain on string at 19″, bile at 20″; severe gastralgia and hunger pains; duodenal alimentation improves condition; in 1915 gastric hemorrhage; duodenal alimentation again used with benefit.
8. Adolph Z. . .	February, 1917, operated twice for severe dyspepsia	Pain, right after meals	HCl+; acidity = 50	20″	24″	Duodenal alimentation brings benefit.

Eight of the patients treated by duodenal alimentation made a complete recovery, not requiring any surgical aid.

Of the other two, A. K. felt considerably improved during the period of duodenal alimentation, but as soon as the tube was removed and nourishment was given in the usual way the pains returned. A provisional diagnosis of severe adhesions with perigastritis was made, and it was necessary to reoperate the wound. The diagnosis was corroborated by the laparotomy, and an anterior gastro-enterostomy was performed.

Patient A. D. S. also derived considerable benefit from duodenal alimentation for several months, but the formation of a new ulcer, with hemorrhages, necessitated surgical intervention.

Duodenal or jejunal alimentation is therefore of distinct value in severe postoperative disturbances of the stomach.

DISCUSSION

Dr. Friedenwald said he had employed duodenal feeding considerably since Dr. Einhorn's introduction of this life-saving method of treatment, having used it in a number of cases after operation. It is a familiar fact that in some cases after gastro-enterostomy the patient is not cured, at least not permanently so, and returns for further treatment. It is a difficult matter to have that patient submit to a second operation, and in the speaker's experience in several instances duodenal feeding has been a great aid, one case, especially, being a man, aged twenty-three years, who had an ulcer of the stomach which had been treated medically for a long period of time, yielding but temporary relief, followed by gastro-enterostomy, with relief for six months. Subsequently returning, the patient was fed by the duodenal tube and has now been well for nearly two years, so that the speaker commends this method of treatment after such operations, before resorting to their repetition.

Dr. Stockton said he had used the duodenal tube in a number of cases after operation, in only one whereof had he observed results worthy of mention, same corresponding rather closely with some described in the paper discussed. That was a case of atony, ptosis, and dilatation, improperly operated (in his belief) by gastro-enterostomy, the patient afterward suffering the usual symptoms described as the "vicious circle."

Under the fluoroscope the food very plainly could be seen passing the pylorus and returning into the stomach through the new opening. This patient's condition was much worse after than before operation, but he was relieved rather promptly by duodenal feeding. After his recovery the patient's health waned to a considerable extent, but he submitted, at the speaker's suggestion, to the undoing of the operation. He is fully well now, but when he gets into a bad condition he is promptly relieved by duodenal feeding, which is assuredly an excellent method in those exceptional cases in which a fresh ulcer forms at the point of operation, and Dr. Stockton believed there was an ulcer at that point in case cited.

Dr. White said he had used the duodenal tube in only two cases after the operation of gastro-enterostomy, and that the results were not very satisfactory. It appears that there may be stomachs in which this proceeding does not work well. The tube went through into the duodenum very well, going perfectly well in one case through the pylorus; in the other case, while the tube went down, there was regurgitation of bile into the stomach, and much distress occasioned.

SOME OBSERVATIONS UPON INTESTINAL BACTERIA IN CHILDREN

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AND

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During the past few years there has been a great revival of interest in the bacteriology of the digestive tract. The investigations of Moro,[1] Tissier[2] and others, especially Herter and Kendall[3] in this country, have explained the discrepancy noted since the days of Escherich, that the number of bacteria in the dejecta is much greater than the number of colonies which develop on our plates. They have demonstrated that the Gram-positive organisms found in smears of the intestinal contents are equally important with the Gram-negative, that they can be freed from the ordinary intestinal bacteria by cultivation in acid broth and that they are just as much obligate inhabitants of the alimentary canal as are Bacillus coli communis and Bacterium lactis aërogenes. The old theory that Bacillus coli is Gram-positive in the intestines and Gram-negative in our cultures was thus proved to be untenable, as was usually suspected. Along with this development of our knowledge, Metschnikow[4] and his followers have attempted to bring about a change in the character of the bacteria in the digestive tract by the administration of food materials containing bacteria producing large quantities of acid from lactose. It was claimed that the ingested bacteria, particularly the so-called Bulgarian bacilli would overcome and displace the species previously multiplying in the intestine, Bacillus

coli and the putrefactive anaërobes. Despite the somewhat extravagant claims of this school of investigators, it has not yet been clearly shown that the ingested organisms are definitely implanted on the intestinal mucosa in man, although Rettger's experiments indicate that such a transplantation may occur in small animals.[5] Furthermore, it should also be indicated that the poisonous action of the putrefactive bacteria in the intestine, while possibly evident clinically in selected cases, had not yet been clearly shown experimentally. Finally there is a good deal of evidence to show that the changes which do occur after the administration of food materials containing Bulgarian bacteria may be due to the chemical constituents of the food, the lactose and the lactic acid, and not due to the bacteria themselves. Nevertheless the idea that profound changes may occur in the bacteria of the intestinal canal as the cause of pathological conditions, or as their accompaniment, and that these changes, particularly the development of a Gram-positive in place of a Gram-negative flora, may be of diagnostic significance and point the way to remedial treatment has become firmly intrenched in the minds of clinicians. This is not without reason in view of the facts which have been brought out recently. There are, however, many contradictions in the published results, and it may be doubted whether our knowledge of the conditions which must exist in such a large and varied area for bacterial development as the gastric and intestinal mucosa is yet sufficiently accurate to permit any exhaustive generalization which may be applied clinically. In view of these considerations it has seemed to us worth while to take up certain phases of the problem again, and in the present investigation we have limited ourselves to one particular inquiry—namely, to what extent differences in the bacterial flora of children can be correlated with the type of food forming the sole or the chief ingredient of the diet. For the solution of this problem we have been allowed to utilize the dejecta of the breast-fed infants in the maternity ward of the Johns Hopkins Hospital and those of the young children in the Harriet Lane Home.

In the early part of our studies we made routine examinations of about fifty (50) children fed on mother's milk, raw and boiled cow's milk, buttermilk and protein milk by the use of the ordinary

media, such as plain and dextrose agar and dextrose broth in the fermentation tube. As might have been expected, we obtained in these cultures practically nothing but Gram-negative bacteria, and no information of value was elicited. It was then decided to make an intensive study of a few cases by a careful microscopic examination of the dejecta and by the adoption of special methods for the cultivation of the various kinds of the microörganisms seen in the smears. It is the result of this examination which we wish to report today.

Smears from the evacuations of children when stained by gentian violet, methylene blue, and by Gram's method reveal six different types of organisms as follows:

1. Small Gram-negative bacilli.
2. Small Gram-positive bacilli.
3. Gram-positive micrococci and streptococci.
4. Gram-positive yeast cells.
5. Large Gram-positive bacilli.
6. Spores of various sizes and shapes.

All these various types of organisms can be cultivated by appropriate methods. With ordinary plates, especially if sugar be present in the medium, the Gram-negative bacilli tend to overgrow and crowd out the other species, and one finds Bacillus coli, Bacterium lactis aërogenes, Bacillus alkaligenes and occasionally some of the rarer liquefiers of the intestines. The small Gram-positive bacilli are chiefly aciduric organisms. They do not appear on agar plates but may be cultivated in acid broth (2 or 3 per cent.), which inhibits the other species. After two or three transfers in this medium, which suffices usually to effect a separation, these aciduric organisms can be obtained in pure culture on agar or blood serum. They grow well on acid agar, and in our experience grow best on acid whey agar. This group evidently represents the aciduric organisms of Moro, Bacillus acidophilus, although at times we have encountered species which resemble those described by Heineman, and which he puts provisionally in the group of Bulgarian bacilli. The yeast cells seldom appear on plain agar plates. They grow out abundantly in acid broth with the aciduric bacilli, but can also be obtained on acid whey agar plates. They grow best on dextrose agar plates

made directly from the dejecta, where they appear after the lapse of six to ten days, when the agar has become highly acid from the growth of Bacillus coli. In such old plates the large, viscid colonies of the yeast cells are easily recognized. The greatest interest attaches to the large Gram-positive bacilli of the intestine. They are of various sizes, sometimes small, measuring one-half to three-fourths by 2 to 3 microns, sometimes large, measuring 1 to $1\frac{1}{2}$ by 3 to 8 microns. Their protoplasm may be regular, as in the smaller form, or highly irregular, as in the large forms, which seem to be made up of spherical bodies. These organisms appear occasionally on agar plates. They can best be cultivated by heating portions of the dejecta in broth to 85° C. for ten minutes, pouring plates at once, and after twenty-four hours' incubation of this broth. By such a procedure an abundant growth of organisms can be obtained which can now be identified as the aërobic spore-bearing bacteria found in soil, dust, water, and milk. In plates poured directly these species have the same morphology as that observed in the smears, and it is sometimes possible upon bacterioscopic examination to give a provisional opinion as to the species which can be cultivated. This is true especially when the large granular bacilli of the megatherium-petasites group are found. The species cultivated from heated material, immediately and after incubation, are naturally much more varied. The size and shape of the spores produced by these organisms are quite characteristic and can usually be correlated with the spores found in the smears. We have now examined the spore-bearing bacteria of the dejecta in about 50 cases, and we are of the opinion that they represent the large Gram-positive bacteria and the spores found in smears. We see no reason to believe that these Gram-positive organisms are anaërobes. The resemblance in morphology of the aërobic spore-bearers cultivated, both in the vegetative state and in the spore states to the vegetative rods and the spores found in smears is so marked as to lead to the opinion that they are the same. We do not deny the possibility that anaërobic bacteria are present in the intestinal tract in probably all cases. We believe, however, that the majority of the Gram-positive rods and the spores probably represent aërobic species. Of special interest is the occasional presence of a small organism

with a round terminal spore looking not unlike the tetanus bacillus. The finding of this organism is sometimes regarded as indicative of intestinal putrefaction, since it has been identified on the basis of its morphology alone as Bacillus putrificus coli of Bienstock. This organism can be cultivated without difficuty, and can now be recognized as one of the common aërobic spore-bearers, Bacillus pseudotetanus.

We have now been able to examine the dejecta of 10 breast-fed babies and of 18 artificially fed children, varying in age from one to ten years. These latter were fed on a mixed diet, on raw and boiled cows' milk, on buttermilk, or on protein milk. The Gram-negative bacilli have shown no variation in the different cases. Except in rare instances they are the most abundant of the species present, and they can always be cultivated on agar plates. The aciduric bacilli were obtained in seven of the ten breast-fed babies and in all of the eighteen children. There was no particular predominance of these organisms except in one case, and their presence, although in small numbers in all of the artificially fed children and in 70 per cent. of the breast-fed infants, suggests that they could always be found were the search extended. In one instance the stool of a normal suckling was made up almost exclusively of long Gram-positive bacilli which could not be cultivated by any method tried. Branching aciduric organisms of the type of Bacillus bifidus were not encountered in our series either in the breast-fed or in the artificially fed children. Gram-positive micrococci and streptococci were found in 6 of the 10 babies and in 10 of the 18 artificially fed children. Many of these were distinctly aciduric; others, however, were streptococci which grow on ordinary plates, while others were evidently Micrococcus ovalis. So far as could be learned no significance is to be attached to the presence of organisms of this group, but the fact that they were isolated from 60 per cent. of the cases leads to the opinion that, like the aciduric bacilli, they are obligate inhabitants of the intestinal canal. Yeasts were obtained in 6 of the 18 children. In 2 of these cases the children were fed on buttermilk, which on culture proved to contain yeasts in great numbers. In 3 other cases milk was the chief article of diet, and in 1 instance the child was being nourished on protein

milk. In 1 case the stool of a six weeks' baby suffering from pyloric stenosis and fed on breast milk was also full of yeasts.

In the dejecta of the breast-fed children aërobic, spore-bearing bacteria were obtained in all but 1 case. They were present in considerable variety in the original smears, even in the youngest nursling, evidently finding their way into the alimentary canal of the child as soon as it begins to swallow. They were not so abundant as to grow out on plates made directly from the dejecta or to any extent from heated material before its incubation. They could, however, always be obtained from this material after incubation for twenty-four hours. In 2 cases the spore-bearing bacteria were markedly increased in these breast-fed children. They appeared in great profusion on our original plates and in plates poured directly from heated material. In one of these cases the stool was made up largely of meconium mixed with a soap suppository, and in the other case the stool was very scanty and material for cultures had to be scraped from the napkin. We do not therefore regard these cases as indicative of any real increase of spore-bearers in the intestinal tract. The spore-bearers found in breast-fed children were chiefly those species which have now been shown to be the pervalent bacteria of our environment. Bacillus cereus and Bacillus albolactus were the most frequent isolations, Bacillus pseudotetanus and Bacillus mesentericus were somewhat less common, while Bacillus subtilis, Bacillus petasites and Bacillus vulgatus were among the rarer findings. This relative proportion of the species is about the same as the proportion established for soil, dust and water, in which Bacillus cereus and Bacillus albolactus are the most abundant.[6] It is interesting to note that often the same organisms were isolated from different cases on the same day, pointing to some sort of a ward infection as their source.

In the artificially nourished children aërobic spore-bearers were found in smears from the dejecta in all instances. In 3 cases they were not isolated from plates made from either the raw or heated material. One of these was a child with pyloric stenosis fed on breast milk and formula, another was a child with pneumonia fed on mother's milk and barley-water, and the third was a child with ileocolitis fed on protein milk and formula. The aërobic spore-

bearers were cultivated in 15 of the 18 cases. Practically the same varieties were found as in the breast-fed children, Bacillus cereus and Bacillus albolactus being the most common. Pseudotetanus bacilli and members of the megatherium and mesentericus groups were also isolated. There was an increase of Gram-positive aërobic spore-bearers in 10 of these 18 cases. The organisms of this character were greatly increased in numbers in the smears, and cultures showed them in abundance in the heated and incubated material. In 6 of these cases these species were so abundant as to appear in large numbers on the plates poured directly from the dejecta. In 8 of these 10 cases the children were fed on protein milk; in 5 of these the stools were normal, in 1 case constipated, in 1 case semi-solid, and in 1 case diarrheal. Of the 2 other cases with an increase in spore-bearers, 1 was suffering from diarrhea and was being fed on buttermilk. The other was a feeding case with normal stools from whom material was examined on four different occasions. No increase in spore-bearers was detected on the first three examinations, at which time the patient was nourished on whole milk, barley-water, and sugar. Subsequently wheat flour and malt soup were added to this diet, and the next examination showed an increase of spore-bearing bacteria. Eight of the artificially fed children failed to show any increase of large Gram-positive bacteria. One of these cases was fed on protein milk and one on buttermilk. The others were receiving either a general diet, breast milk mixed with barley-water, or cows' milk and barley-water. We thus see that with two exceptions an increase of aërobic spore-bearing bacteria in the intestinal discharges, Gram-positive in character, is regularly associated with a diet of protein milk or buttermilk.

The question now arises as to the explanation of this association which we believe to be quite definite. Does the diet of protein milk or buttermilk, for instance, so change the character of the intestinal contents as to lead to profound alterations in the conditions for bacterial development, or is there a possibility that these organisms make their way into the alimentary canal with the food and find there either a temporary or a permanent nidus for development? We believe this latter explanation to be the correct one. To throw some light upon this question a bacteriological examination

of the various foods employed in the Harriet Lane Home was undertaken, including pasteurized milk, protein milk, buttermilk and farina. All these articles of diet were found to be infected with aërobic spore-bearing bacteria, the spores of which are capable of withstanding the heat employed in ordinary cooking. The bacteria found in protein milk and in buttermilk were especially abundant, Bacillus cereus and Bacillus albolactus being the predominant types. In the heated milk they were somewhat less common, the same species predominating. Farina was relatively free from bacteria and in the samples examined contained chiefly pseudotetanus bacilli. The various articles of diet contained the following species of bacteria:

PROTEIN MILK

Bacillus cereus.
Bacillus albolactus.
Bacillus mesentericus.
Streptococci.
Moulds.

HEATED MILK

Bacillus cereus.
Bacillus albolactus.
Bacillus mesentericus.
Micrococci.
Moulds.

BUTTERMILK

Bacillus cereus.
Bacillus albolactus.
Bacillus mesentericus.
Yeasts.
Moulds.

FARINA

Bacillus pseudotetanus.
Bacillus cereus.
Bacillus albolactus.
Bacillus mesentericus.
Moulds.

From the results of this examination it may be seen that the bacteria with which the food is infected are almost the same as those found in the dejecta of the children fed on these foods. Bacillus cereus and Bacillus albolactus are the most common, while Bacillus mesentericus and Bacillus pseudotetanus also appear. The relative proportion of the species encountered in the foods is also strikingly similar to that established for the dejecta. We are therefore inclined to the opinion that the presence of aërobic spore-bearing bacteria, Gram-positive in character, in the dejecta of children, is to be attributed to their mechanical introduction with the richly infected food. This we believe particularly striking in the cases in which the children are fed on protein milk and buttermilk. That a change in the chemical ingredients of the food employed may be the causative factor in the appearance of the large Gram-positive bacteria in the dejecta is not ruled out by our methods of investigation, and for the present our conclusion cannot be regarded as anything more than a well-defined opinion. We hope to clear up this point in future studies. We see no reason to believe that the presence of large Gram-positive organisms is indicative of anaërobic putrefaction, however, nor is it of any diagnostic value, since it occurs with a variety of clinical conditions. It is possible that we have here an actual substitution of bacterial species in the intestine; but whether this substitution is temporary or permanent is not clear from the work thus far completed. It is interesting to note that the results of this work lend no support to the old contention of Flügge[7] that the resistant spore-bearing organisms which survive in boiled milk may pass through the acid gastric juice, multiply in the alkaline contents of the lower bowel, and by their toxic products set up diarrheal conditions. The presence of normal, constipated, or loose stools in cases in which there is a great increase in aërobic spore-bearers indicates that these organisms may be regarded as practically harmless in the alimentary canal even if they be present there in large numbers. Finally, our results indicate that one should be extremely cautious in drawing any conclusions which have a clinical bearing from a bacteriological examination of the dejecta unless a study of the bacteria in the ingested food be made at the same time.

CASES EXAMINED (BREAST–FED CHILDREN).

CASE 1.—Handy, three or four days; stool normal.

Smears showed Gram-negative bacilli, Gram-positive cocci, and a few large Gram-positive bacilli. Cultures revealed Bacillus coli, aciduric cocci, and four spore-bearers in small numbers, Bacillus cereus, Bacillus pseudotetanus, Bacillus mesentericus, and Bacillus petasites. No increase of spore-bearers.

CASE 2.—Jenkins, four days; stool normal.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and cocci and large Gram-positive bacilli and oval spores. Cultures revealed Bacillus coli, Bacillus cereus, and Bacillus albolactus in considerable numbers. This stool was small, chiefly meconium, and in making the cultures the material had to be scraped from the napkin. The increase of spore-bearers may be explained on this basis.

CASE 3.—Phillips, seven days; stool normal.

Smears showed chiefly Gram-negative bacilli, Gram-positive cocci and large Gram-positive bacilli with some terminal-spored organisms. Cultures revealed Bacillus coli, aciduric bacilli and Bacillus cereus in great numbers. This stool was obtained by means of a soap suppository and the increase of spore-bearers may have been due to this factor.

CASE 4.—Pancoast, fifteen days; stool normal.

Smears showed Gram-negative bacilli and a few large Gram-positive bacilli. Cultures gave Bacillus coli and Bacillus cereus. No increase of spore-bearers.

CASE 5.—Bialecka, five days; stool normal.

Smears showed Gram-negative bacilli, small Gram-positive bacilli, large Gram-positive bacilli, and large cocci. Cultures revealed Bacillus coli, aciduric cocci, Bacillus cereus and Bacillus mesentericus. No increase of spore-bearers.

CASE 6.—Keen, twelve days; stool normal.

Smears showed Gram-negative bacilli and small Gram-positive bacilli. Cultures revealed Bacillus coli, aciduric bacilli and cocci, Bacillus pseudotetanus and Bacillus petasites. No increase of spore-bearers.

CASE 7.—Goldstein, five weeks; stool normal.

Smears showed Gram-negative bacilli, small Gram-positive bacilli, and cocci. Cultures showed Bacillus coli, aciduric bacilli, and cocci, Bacillus cereus and Bacillus pseudotetanus. No increase of spore-bearers.

CASE 8.—Waters, nineteen days; stool normal.

Smears showed Gram-negative bacilli, Gram-positive cocci. Cultures revealed Bacillus coli, aciduric bacilli and cocci, and Bacillus pseudotetanus. No increase of spore-bearers.

CASE 9.—Mitchel, eight months; stool normal.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and

large Gram-positive bacilli. Cultures revealed Bacillus coli, aciduric bacilli and cocci and a variety of spore-bearers in small numbers, Bacillus cereus, Bacillus pseudotetanus, Bacillus vulgatus, and Bacillus mesentericus. No increase of spore-bearers.

Case 10.—Ritz, six weeks, H. L. H., pyloric stenosis; stool normal; breast-fed.

Smears showed very few Gram-negative bacilli, many thin rather long Gram-positive bacilli, a typical Gram-positive flora. No large Gram-positive organisms found. Cultures revealed aciduric cocci and aciduric bacilli of a different morphology from that of the organisms seen in the smear. Yeast cultivated. No spore-bearers found.

ARTIFICIALLY FED CHILDREN

Case 1.—Naomi Sparks, three months, H. L. H., feeding case; stool normal. Diet whole milk, barley-water and cane-sugar. Stools examined on four occasions. Smears showed small Gram-negative bacilli, small Gram-positive bacilli and micrococci, large Gram-positive bacilli and terminal spored organisms. Cultures showed Bacillus coli, aciduric bacilli and micrococci and yeasts together with Bacillus cereus, Bacillus albolactus and Bacillus pseudotetanus. No increase of spore-bearers. In this case there was a good deal of variation in the amount of sugar in the diet, and wheat flour and malt soup were added to the whole milk and barley-water, after which the spore-bearers were definitely increased.

Case 2.—Baby, six weeks, H. L. H., diarrhea; stools numerous and watery. Diet, breast milk and buttermilk.

Smears from the stool showed Gram-negative bacilli, small Gram-positive bacilli, and large Gram-positive bacilli. Cultures showed Bacillus coli, aciduric bacilli, and Bacillus cereus. Spore-bearers increased.

Case 3.—Kiakenal, four years, H. L. H., intestinal indigestion; stool large, semisolid, foul, pasty, and full of fat and undigested meat fibers. Diet, protein milk and junket. Two examinations.

Smears showed Gram-negative bacilli, small Gram-positive bacilli, large Gram-positive cocci, large Gram-positive bacilli. Cultures showed Bacillus coli, aciduric bacilli and micrococci, and Bacillus cereus. No increase of spore-bearers in the first examination on admission to hospital. On second examination after the diet of protein milk and junket was established, the spore-bearers were definitely increased.

Case 4.—Poulsky, three months, H. L. H., fatal diarrhea; stools numerous, watery, containing a small amount of mucus and numerous curds varying in size from that of a small pea to that of a small lima bean. The vomitus contained the same curds. Diet, protein milk, and buttermilk. Stools examined three times.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and cocci, large Gram-positive bacilli. Cultures revealed Bacillus coli, acidurice bacilli and micrococci and yeasts, together with Bacillus cereus. Bacillus albolactus and Bacillus mesentericus. Spore-bearers definitely increased. The curds showed a few Gram-negative bacilli, many Gram-positive cocci and yeasts, and a great predominance of Gram-positive bacilli. Cultures from them revealed yeasts, and the three species mentioned above in overwhelming numbers. Their presence in the vegetative state in the curds is suggestive of an actual multiplication in the passage of the curds through the alimentary canal.

Case 5.—Hoska, two years, H. L. H., acidosis; stools frequent, foul, watery, and bloody. Diet, buttermilk and farina. Two examinations.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and micrococci, large Gram-positive bacilli, yeasts and spores. Cultures revealed Bacillus coli, aciduric bacilli, yeasts, Bacillus cereus, Bacillus albolactus and Bacillus mesentericus. No increase of spore-bearers.

Case 6.—Durkin, H. L. H., fatal acidosis; stools numerous and watery. Diet general and restricted.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and cocci, large Gram-positive bacilli, yeasts, oval spores, and terminal-spored bacilli. Cultures revealed Bacillus coli, aciduric bacilli, together with Bacillus cereus, Bacillus subtilis, and Bacillus albolactus. No increase of spore-bearers.

Case 7.—Wirtz, one year, H. L. H., pneumonia; stools large and constipated. Diet, heated milk, barley-water, farina, and orange juice.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and cocci, large Gram-positive bacilli, spores, and yeasts. Cultures revealed Bacillus coli, Bacillus lactis aërogenes, aciduric bacilli and cocci, yeasts, and Bacillus cereus. No increase of spore-bearers.

Case 8.—Winn, seven months, H. L. H., pneumonia; stools frequent, watery. Diet, protein milk.

Smears showed Gram-negative bacilli, Gram-positive cocci, large Gram-positive bacilli. Cultures revealed Bacillus coli, Bacillus lactis aërogenes, aciduric bacilli and cocci, together with Bacillus cereus. No increase of spore-bearers.

Case 9.—B. W., five months, H. L. H., eczema; stool normal. Diet, milk, barley-water, sugar and farina.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and cocci and large Gram-positive bacilli. Cultures revealed Bacillus coli, aciduric bacilli and cocci, yeasts, together with Bacillus cereus and Bacillus pseudotetanus. No increase of spore-bearers.

Case 10.—Liebergott, eight months, H. L. H., feeding case after diarrhea; stools normal. Diet, protein milk and buttermilk.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and large Gram-positive bacilli. Cultures revealed Bacillus coli, aciduric bacilli and cocci, together with Bacillus cereus, Bacillus albolactus and Bacillus pseudotetanus. Spore-bearers increased.

Case 11.—Harris, three months, H. L. H. Diet, protein milk.

Smears showed Gram-negative bacilli, small Gram-positive bacilli and cocci, large Gram-positive bacilli. Cultures revealed Bacillus coli, aciduric bacilli, yeasts and several of the common spore-bearers. Spore-bearers increased.

Case 12.—Boehm, ten months, H. L. H., acidosis; stools large and constipated. Diet, protein milk and dextro-maltose.

Smears showed small and medium-sized Gram-negative bacilli, Gram-positive diplococci or short streptococci, small Gram-positive bacilli and large Gram-positive bacilli in considerable numbers. These last were of various sizes and shapes. Some had round ends, others square ends, and many showed degenerated cytoplasm. A few very large Gram-positive organisms were found with large subterminal spores. Small spores of the subtilis or mesentericus type were also found. Cultures revealed Bacillus coli, aciduric bacilli, Micrococcus ovalis, and Bacillus subtilis. The plates from the raw material showed no increase of spore-bearers. Plates from the heated material before and after incubation showed many colonies of Bacillus subtilis.

Case 13.—Uraigle, eight months, H. L. H., acidosis and polyuria; stools normal. Diet, protein milk and dextro-maltose.

Smears showed small and medium-sized Gram-negative bacilli, small Gram-positive bacilli, small and large Gram-positive diplococci, and a great increase of large Gram-positive bacilli. These last were of various sizes and shapes, some with round ends, others with square ends resembling Bacillus cereus or Bacillus megatherium in morphology. Cultures revealed Bacillus coli, Micrococcus ovalis, aciduric bacilli and cocci, and Bacillus subtilis. No increase of spore-bearers on plates made from raw material. Bacillus subtilis in great profusion on plates made from heated material, both before and after incubation.

Case 14.—Ament, seven months, H. L. H., pneumonia; stools constipated. Diet, breast milk and barley-water.

Smears showed small and medium-sized Gram-negative bacilli and diplococci, small Gram-positive bacilli, and diplococci. No large Gram-positive organisms seen. Cultures revealed Bacillus coli, aciduric bacilli and cocci. No spore-bearers isolated from raw material or from heated material before or after incubation.

Case 15.—Queirein, seven to eight months, H. L. H., ileocolitis; stools loose. Diet, protein milk and formula.

Smears showed small and medium-sized Gram-negative bacilli, Gram-

positive diplococci, and large Gram-positive bacilli. The latter were abundant but not increased. Cultures revealed Bacillus coli, aciduric bacilli and micrococci, and terminal-spored bacilli growing in acid broth. No spore-bearers cultivated from raw material or from heated material either before or after incubation.

Case 16.—Seto, nine to twelve months, H. L. H., furunculosis with possible diagnosis of scurvy; stools normal. Diet, protein milk, junket, and orange juice.

Smears showed small and medium-sized Gram-negative bacilli, small Gram-positive bacilli, Gram-positive diplococci and large Gram-positive bacilli with occasionally degenerated cytoplasm. Large Gram-positive bacilli increased in number in the smears. Cultures revealed Bacillus coli, aciduric bacilli and Bacillus subtilis. No increase of spore-bearers on plates from raw or heated material.

Case 17.—Caplan, nineteen months, H. L. H., anemia and throat infection; stools normal. Diet, protein milk.

Smears showed small and medium-sized Gram-negative bacilli, small Gram-positive bacilli and diplococci and large Gram-positive bacilli much increased in number. The latter were in many instances sporulating with spores in the center and degenerated cytoplasm. Cultures revealed Bacillus coli, aciduric bacilli, and Bacillus subtilis. No increase of spore-bearers on plates from raw or heated material.

Case 18.—Schneider, two months, H. L. H., pyloric stenosis; stools normal. Diet, breast-milk and formula.

Smears showed small Gram-negative bacilli, rather small, long and thin Gram-positive bacilli, Gram-positive diplococci, and a few large Gram-positive bacilli with subterminal spores. Cultures revealed aciduric bacilli and cocci and an unknown aciduric spore-bearer. No other spore-bearers isolated from either the raw or heated materal.

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DISCUSSION

Dr. Welch said that while he thought the author's conclusion as to the ingestion of the abnormal bacteria was doubtless right as to its being a very important factor, it did not, to him, seem that the experiments or observations were conducted in such a way as to definitely decide the point as to the relative importance of the chemical ingredients of the ingested food and of the bacterial flora which might be contained therein. There is no question but that alterations of the chemical ingredients represent a very important factor in determining the character of the intestinal flora. It had always seemed to him that a very striking instance of the influence of the environment and also as indicating the presence of intestinal bacteria which ordinarily are not revealed either in cover-slides or by the culture method is the character of the bacterial flora in the cases of perforative peritonitis. Of course, in some of those instances there is already an abnormal flora, but not necessarily so; but in the speaker's belief the flora we find in the peritoneum in cases of perforative peritonitis demonstrates the germs which can be recognized as coming from the intestinal canal. It also shows the larger role which the streptococcus plays in those cases, and the proteus bacillus, and occasionally the gas bacillus—bacteria which are not found or are not particularly predominant in the intestine. Dr. Welch had never, he thought, seen the point sufficiently emphasized as to the inferences which might be drawn from the characters of the bacterial flora in cases of perforative peritonitis as indicative of the bacterial flora in the normal intestine.

OBSERVATIONS ON THE TREATMENT OF MYELOCYTIC LEUKEMIA BY RADIUM

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Renon, Degrais and their associates (1910) were the first to treat myelocytic leukemia by means of radium exposures over the enlarged spleen. In 1913 they reported 5 cases. In the first case satisfactory remissions were obtained with five series of exposures over a period of two years. Death occurred two years and two months after the first treatment. In the case of their second patient a satisfactory result was obtained over a period of nine months with two series of exposures. Death occurred twelve months after the first treatment. Two patients were in good condition six months after their first treatment. The fifth patient had been splenectomized prior to the use of radium, a 2800 gm. spleen having been removed. Following the splenectomy the leukocytes fell to 27,000 but subsequently rose to 143,000. Benzol was used without apparent effect. The splenic area was then exposed to radium and this procedure was curiously followed by a reduction of the leukocytes to 21,500. It was not noted by the authors that the reduction may have been a late effect of benzol; it may, on the other hand, have been due to the direct effect of radium on the large amount of blood in the abdominal cavity. Radium was next applied over the thighs, but the leukocytes rose to 81,600. Radium had been applied over the thighs in one other case of this series without favorable result.

Renon and Degrais mentioned that twelve patients had been treated by other French observers with the initiation of favorable remissions.

In the English literature a few cases have been reported in which radium exposures were followed by remissions. Similar results have been obtained by Peabody and by Burnham in this country in a large series of unpublished cases.

In May, 1916, before the Association of American Physicians, Ordway presented a complete and instructive discussion concerning radium therapy in myelocytic leukemia and placed on record a detailed study of one of his cases in which a remarkable remission had been brought about by means of radium emanations. In this case the patient had been formerly resistant to both the roentgen rays and benzol. Death occurred, however, fifteen months after the recognition of the disease.

The results of these various observers lead only to the conclusion that it is important to make use of this method of treatment when possible in order to initiate a remission in a disease with so unfavorable a prognosis. Our own experience from May 15, 1916, to April 1, 1917, comprises a series of thirty consecutive cases of myelocytic leukemia which have been treated by means of the surface application of radium element over the spleen.

Method of Application. In some instances in this series we used 50 mg., and in others 100 mg. of the radium element in tubes. The enlarged spleen was mapped out into squares in the manner described by Ordway and the radium exposed over each area for periods of three or four hours. The total length of time for each series of applications varied from twelve to forty-eight hours; usually, however, the time was from twenty-four to thirty-six hours. Patients remained in bed during exposure. In the early cases the protection consisted only of 2 mm. of lead beneath the radium and 2 mm. of lead over the radium. The radium was held in place by means of adhesive plaster. Superficial burns resulted, but they were never serious and healed without difficulty. As previously pointed out by Ordway, our experiences demonstrated that the skin formerly traumatized by adhesive plaster was especially susceptible to burn. After adding $\frac{1}{2}$ inch of wood beneath the 2 mm. lead screen we obtained results equally satisfactory with only occasionally a slight burn. The radium may be raised so far from the skin by means of gauze that little result is obtained from the exposures. When a

satisfactory response does not occur we reduce the protection even to the point of burning the patient. Dr. W. J. Tucker, working with me, devised a biscuit-shaped block which has been used routinely for several months. This consists of ½ inch of wood, 2 mm. of lead, ½ inch of wood bored to receive the tubes of radium, and above this 2 mm. of lead and another ½ inch of wood. The block is held in position by means of a simple canvas belt. An endeavor is made to concentrate the fire through the most massive portions of the spleen.

Clinical Experience. For convenience of presentation our thirty cases have been classified with respect to the size of the spleen at the time of the original examination. The degree of splenic enlargement is denoted by the Scale 1–4. Scale 4 represents a spleen of enormous size extending beyond the midline and into the right ileac fossa, practically filling the abdomen; Scale 3, a spleen the edge of which extends well to the right of the navel; Scale 2, a spleen extending beyond a point midway between the costal edge and the umbilicus; Scale 1, a spleen which is easily palpable or which extends only a couple of inches from the costal edge. Spleens having unusual contour or position have been represented by their approximate equivalents in this scale.

TABLE 1. MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

Spleen—Scale 1 (slightly enlarged)

No.	Previous leukocyte count.	Previous neut. myelocyte percentage.	Subsequent leukocyte count.	Subsequent neut. myelocyte percentage.	Reduction in size of spleen.	Time between counts.	Mg. hours.	Number of treatments.
173312	12200	11.0	3800	1.7	1 to normal	46 days	5400	4
175574	97000	19.0	6600	1.0	1 to normal	39 days	3800	2
186558	207000	27.7	12800	8.3	1 to normal	40 days	6600	5
169876	96000	20.7	8400	2.7	1 to normal	61 days	2000	2

There were four patients with spleens in the Scale 1 group (small but easily palpable spleens). (Table 1.) The spleen was reduced to approximately normal size in these four patients in from thirty-nine to sixty-one days, after from 2,000 to 6,600 mg. hours of radium given in from two to five series of exposures. The leukocytes in one instance fell from 207,000 to 12,800 in forty days, and in another

from 97,000 to 6,600 in thirty-nine days. The general condition and the anemia in all these patients were definitely improved.

TABLE 2.—MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

Spleen—Scale 2 (moderately enlarged)

No.	Previous leukocyte count.	Previous neut. myelocyte percentage.	Subsequent leukocyte count.	Subsequent neut. myelocyte percentage.	Reduction in size of spleen.	Time between counts.	Mg. hours.	Number of treatments.
160937	188000	28.0	9400	0.0	2 to normal	50 days	2600	2
	107600	18.7	68000	18.3	1 to normal	20 days	800	1
159989	329000	29.7	7000	2.3	2 to normal	54 days	4300	2
	62000	14.3	15800	3.3	1 to normal	31 days	4450	3
181494	125600	7.3	3800	0.3	2 to normal	70 days	5400	5
183015	229000	19.0	81800	11.3	2 to 1	21 days	5350	4
187921	8200	4.7	6200	1.7	2 to 1	11 days	3600	2
172156	389000	47.0	147000	33.3	2 to 1+	13 days	2000	2
	343000	25.3	42600	9.3	2 to 1	23 days	7000	4
173445	214000	29.0	22000	8.0	2 to 1+	48 days	5400	3

There were 7 patients with spleens in the Scale 2 group (spleens extending nearly or quite to the region and level of the navel). (Table 2.) In 3 of the 7 the spleen was reduced to approximately normal size in from fifty to seventy days after from 2,600 to 5,400 mg. hours of radium given in from two to five series of exposures. Two of these patients were discharged at the end of fifty and fifty-four days from the time of the first exposures, their leukocyte counts having fallen from 188,000 to 9,400 and 329,000 to 7,000. They returned in four months and in two months respectively with leukocyte counts of 107,600 and 62,000 and their spleens slightly enlarged. Reduction again occurred to approximately normal size in twenty and thirty-one days respectively with, in one instance, one series of exposures, and in the other, three. The patients were in such good general condition that it was thought inadvisable to extend the treatment to the point of reducing the leukocytes to a normal count. As has been stated, 3 of the 7 patients in this group were discharged with approximately normal size spleens. In the remaining 4 the spleens were reduced to Scale 1.

In one case (187921) the diagnosis was somewhat doubtful. The history was satisfactory for myelocytic leukemia but the leukocyte count was in the neighborhood of 8,000 cells of which 4.7 per cent. were myelocytes. It is quite probable, however, that the case will prove itself to be one of myelocytic leukemia.

In another case of this group, one of long standing (172156) the improvement in the general condition was not commensurate with the reduction in the size of the spleen and the leukocyte count.

TABLE 3.—MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

Spleen—Scale 3 (moderately enlarged)

No.	Previous leukocyte count.	Previous neut. myelocyte percentage.	Subsequent leukocyte count.	Subsequent neut. myelocyte percentage.	Reduction in size of spleen.	Time between counts.	Mg. hours.	Number of treatments.
173772	360000	29.3	5800	0.7	3 to 1	69 days	8000	5
177183	712000	39.7	18200	6.7	3+ to 1	122 days	9400	6
183919	24300	12.7	16000	20.3	3 to 1	41 days	5800	5
188262	222000	22.3	22000	9.3	3 to 1	22 days	9000	3
170257	389000	40.3	20900	21.7	3 to ?	10 days	1800	1
168142	88000	50.7	34600	27.3	3 to 2	12 days	3150	2
169360	142000	40.3	9800	9.3	3+ to 2	43 days	3600	2
173740	29000	20.3	15200	19.3	3+ to 2	7 days	1400	1
173747	8200	15.7	1600	2.3	3 to 2	98 days	3400	3
181399	395000	32.7	19000	0.0	3 to 2	41 days	7750	8
52388	258000	32.7	108000	27.0	3+ to 3	12 days	4450	2

There were 11 patients with spleens in the Scale 3 group (very large spleens extending well beyond the level of the navel). (Table 3.) Four of the 11 spleens were reduced to Scale 1, or were easily palpable in from twenty-two to one hundred and twenty-two days after from 5,800 to 9,400 mg. hours in from three to six series of exposures. Six of the 11 spleens were reduced to Scale 2, or extended approximately midway between the costal edge and the navel. In one there was only a slight reduction. This patient, however, was in very poor physical condition and treatment was not continued.

One patient of Scale 3 group (173747) gave a satisfactory history for leukemia but the leukocyte count was low—8,200 with 15.7 per cent. myelocytes. The leukocyte count became reduced, after three series of exposures, to 1,600 cells of which 2.3 per cent. were myelocytes; the size of the spleen was little changed. In the series as a whole an extreme leukopenia such as occurred in this case has been guarded against. The patient began to show changes in the mechanism of coagulation, and slight epistaxis occurred. Transfusion was done and he improved immediately. Three months later he had a definite leukocytosis which further corroborated the diagnosis. Another patient of this group (169360) showed a marked hemorrhagic tendency at the time of the first examination, *i. e.*,

epistaxis, hematuria, petechial and purpuric eruptions and a very toxic condition. After two series of exposures, a total of 3,600 mg. hours, over a period of forty-three days, all hemorrhage ceased, the patient's general condition improved remarkably, the leukocytes were reduced from 142,000 to 9,800, and the spleen was considerably smaller. It has been repeatedly noted following radium treatment that the hemorrhages cease when the condition of the patient becomes improved. A very rapid improvement and reduction of the leukocyte count occurred in one patient (170257) in whom after one series of exposures, 1,800 mg. hours, the leukocyte count became reduced in ten days from 389,000 to 29,900.

TABLE 4.—MYELOCYTIC LEUKEMIA—RADIUM TREATMENT

Spleen—Scale 4 (huge)

No.	Previous leukocyte count.	Previous neut. myelocyte percentage.	Subsequent leukocyte count.	Subsequent neut. myelocyte percentage.	Reduction in size of spleen.	Time between counts.	Mg. hours.	Number of treatments.
175791	918000	25.7	19600	13.0	4 to 1	31 days	8300	5
162899	280000	28.0	11600	0.0	4 to 2	57 days	5300	3
178536	773000	35.0	25000	3.7	4 to 1	75 days	7700	5
180499	604000	28.3	5600	0.7	4 to 1	46 days	10000	6
176684	215000	16.3	8200	4.3	4 to 1	26 days	4600	3
168742	16400	17.0	4200	4.3	4 to 2	33 days	4500	1
175480	470000	33.3	157000	10.3	4 to 3	105 days	7550	7
166824	644000	43.0	30400	34.7	4 to 3	99 days	4350	3

There were 8 patients with spleens in the Scale 4 group (enormous spleens). (Table 4.) The most remarkable results were seen in some of the cases of this group. In 4 of the 8 patients the spleen became reduced from Scale 4 to Scale 1 in from twenty-six to seventy-five days after from three to six series of exposures, totaling from 4600 to 10,000 mg. hours. In the remaining 4 cases there was a very considerable reduction in the size of the spleen and in the leukocyte count, in spite of the fact that 2 of the patients were *in extremis* and no results would ordinarily have been expected from treatment. In one instance in this group the leukocyte count was reduced from 918,000 to 19,600 in thirty-one days after five series of exposures. In another instance the leukocyte count was reduced from 773,000 to 25,000 in seventy-five days after five series of exposures. In this latter patient the reduction of the spleen was remarkable.

Another patient of this group (168742) presented a satisfactory history for leukemia while the leukocyte count was only 16,400, of which 17 per cent. were myelocytes. It is apparently not of rare occurrence to observe in myelocytic leukemia a huge spleen without extreme leukocytosis, the case being of more chronic type with longer history; this type of case is apt to show a less marked remission as the result of radium treatment.

It is not possible, without extended discussion, to follow in detail the individual cases of the series; however, the temporary effect of the treatment by radium exposures has been demonstrated. The ultimate results cannot be summarized at this time, but there is no reason to believe that the effect will be other than temporary. In 14 of the 30 cases after a marked reduction of the size of the spleen had been brought about by means of radium, splenectomy was done without operative mortality. The postoperative course of these cases cannnot be satisfactorily discussed at present.

The Differential Count. The reduction not only of the absolute number but also of the relative percentage of myelocytes, is most striking after radium treatment. As a less extreme and quite representative example one instance (168742) may be cited in which the myelocytes fell from 29.7 per cent. of 329,000 cells to 2.3 per cent. of 7000 cells or from approximately 98,000 cells to 140 cells. It has always been possible to find myelocytes in the smears on prolonged search, though they have occasionally been absent upon the routine differential count.

The reduction of the number of neutrophilic polynuclears is also striking. The relative percentage remains approximately the same before and after treatment, but the reduction of the absolute polynuclear count is very great; for example, in the case previously cited a reduction from 57 per cent. of 329,000 cells to 70.7 per cent. of 7000 cells or from approximately 187,000 cells to 5000 cells.

Although the relative percentage of small lymphocytes increases after reduction of the leukocyte count there is nevertheless a reduction of the absolute count to approximately one-tenth of the original number of cells. The relative percentage of large mononuclears increases after treatment but some of these are without doubt myeloblasts.

Reactions following the Use of Radium. The immediate reactions of radium treatment in the series have been infrequent and mild. Large doses have not been used and in most instances the series of exposures has been of short duration. Only once did vomiting occur, and it was not severe. In 6 instances there was more or less complaint of nausea with weakness; in 2 there was headache and in 1 there was quite a persistent complaint of backache.

Radium is a powerful element and it is necessary to study carefully the results of treatment in order to avoid overexposure and possible harm. Repeated applications of radium once a week for several weeks may initiate a severe anemia with leukopenia. If the red blood cells fall below 2,500,000 transfusion should be considered and radium treatment temporarily discontinued. When there is reduction of the spleen and reduction of the leukocytes one's enthusiasm may lead to overapplication. As a rule we have been content to have the leukocytes fall to 20,000 or 15,000 cells. With a definite leukopenia there seems to be much more likelihood of the occurrence of a crisis with severe anemia and hemorrhage. The anemia may then simulate the primary type, with normoblasts and megaloblasts present. We have noted a temporarily increased fragility of the red blood cells shortly after radium exposure. It is also probable that there is a reduction of platelets after excessive radium treatment. We have learned quite definitely the necessity for the timely use of transfusions in connection with radium treatment. In general, as patients with leukemia approach a serious condition, severe anemia develops. If this anemia can be combated by means of transfusions life can frequently be prolonged.

Improvement in the General Condition. The improvement in the general condition in some instances is nothing short of remarkable, even after one or two series of exposures. The appetite returns, the toxemia becomes ameliorated and the strength rapidly increases. The improvement in the general condition does not seem to be the result of a rapid improvement of the anemia but is probably due to a reduction of the toxemia and leukocytosis and an increase of appetite. Very marked improvement of the general condition is frequently seen with only slight improvement of the hemoglobin and red cell count. A gain in weight results in spite of the rapid reduction in the size of

the spleen. A certain degree of improvement occurred in all the 30 patients treated. In 26 there was marked improvement, and in 13 of these a very remarkable improvement.

Cases in which the Anemia was not Improved. There were 5 patients in whom at one time or another during the course of the radium treatment a definite improvement in the hemoglobin and in the red blood cells did not occur. Three of the 5 were in extremely bad condition. One was so ill that after one treatment radium was discontinued. Another was a severe bleeder and was very resistent to treatment, although the bleeding finally ceased and general improvement occurred without transfusion. The third responded fairly well to a first series of exposures, but returned in a few weeks with severe anemia and ascites. The remaining 2 of the 5 patients with severe anemia were examples of the results of long-continued exposures. Leukopenia and severe anemia together with a petechial eruption and epistaxis developed. Transfusions were resorted to, and the patients are both now in very good general condition.

Hemorrhage. The effect of radium exposures on hemorrhage in myelocytic leukemia is important. It can be stated definitely that hemorrhages have very promptly ceased after improvement has been initiated by means of radium. Fourteen patients gave a previous history of hemorrhage. In many instances bleeding had followed the extraction of a tooth. Epistaxis was a more common form of spontaneous hemorrhage. Purpura, petechiæ and melena also occurred. In only two instances did hemorrhage follow radium treatment when it had not occurred previously. In all of the other hemorrhagic cases the hemorrhage ceased after the first, second or third exposures. One patient who was a very severe bleeder ceased to bleed after two series of exposures. The two patients who bled only after radium treatment had developed a severe anemia and a leukopenia, and hemorrhages were slight; in one instance epistaxis and in the other petechiæ over the legs. Transfusions were immediately resorted to, with satisfactory results.

Summary. 1. Thirty consecutive cases of myelocytic leukemia were treated by means of the surface application of radium element over the enlarged spleen. A dosage of 50 and 100 mg. was used. The protection finally adopted was 2 mm. of lead and $\frac{1}{2}$ inch of wood.

The splenic area was mapped out into squares after the manner described by Ordway, and the radium was applied over each square for from two to four hours, with a total exposure usually of twenty-four to thirty-six hours. The exposures were repeated every week until a satisfactory remission was obtained.

2. A certain degree of general improvement, together with reduction of the size of the spleen and of the leukocyte count, occurred in every instance, even in the most advanced and toxic cases. Marked temporary improvement occurred in 26 patients and a remarkable improvement in 13. It is impossible to satisfactorily discuss the subsequent histories of these cases at this time.

3. Hemorrhage ceased as a rule after one or two series of exposures. In two instances hemorrhage occurred after radium exposures when it had not occurred previous to treatment. In these instances the hemorrhage seemed to be the result of overexposure; an anemia also developed; both the hemorrhage and the anemia were successfully combated by means of transfusion.

4. In 25 patients there was definite improvement of the anemia concomitant with the improvement of the general condition. The reduction of the number of leukocytes was due chiefly to not only an absolute but also a striking relative fall in the myelocytes; there was a striking fall in the absolute count of polynuclears while their relative percentage remained approximately the same. There was also a marked fall in the absolute count of small lymphocytes.

5. Surface exposures of radium over the spleen of myelocytic leukemia usually effect a very rapid reduction of the size of the spleen, a fall of the leukocyte count, improvement in the general condition, and together with transfusion, constitute at present a most effective measure in the treatment of the disease.

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DISCUSSION

Dr. Stengel stated the chairman had asked him by way of discussion to make some report of experiences he had had with *x*-ray treatment of leukemia, otherwise, perhaps, he should not have dared to make any remarks about the cases. There does seem, of course, to be a close resemblance in the manner of treatment, and there should be a close relation in the results obtained by these two methods. His own experience with radium was practically *nil*, having been confined to a few cases which had been treated by others. He and his associates had treated by *x*-rays about 50 cases, consisting, say, of 33 cases of myeloid leukemia, 9 cases of myelocyic leukemia, and 9 cases of lymphatic leukemia. In the earlier days the treatment by *x*-rays was directed over the spleen, a fact well-known—a method subsequently abandoned because of the reactions. In the series mentioned reactions occurred similar to those referred to in the paper, namely: headache, nausea, vomiting, and minor reactions. Additionally there were a few severe reactions in the form of chill, but as to the classic effect upon the spleen obtained in the earlier method of treatment, said series was not studied in nearly the detail Dr. Giffin had indicated, the condition of the spleen not having been followed very closely, the treatment over the spleen having a number of years ago been, at least as a primary measure, abandoned.

From memory of a few of his cases Dr. Stengel's general impression was that there was not, in the cases of Dr. Giffin, a decidedly more evident reduction of the spleen than observed from the method of treatment more recently used by the speaker and his associates, consisting of treatment over the bone and, after the treatment has progressed a certain distance, over the spleen; and, so far as the blood pictures were concerned their results, it seemed to him, were practically comparable to the results obtained with radium. Of the myeloid form of leukemia, all but 2 of 24 cases showed a considerable improvement in the blood count; that is to say, a marked reduction in the number of leukocytes. In 8 of the cases the blood count, so far as it concerned the leukocytes, returned to normal; and in 3 of the cases the blood was examined by expert hematologists without knowledge of the previous history of the cases and with failure, on their part, to recognize the previous existence of leukemia. In 2 of these 3 cases, upon being informed that a leukemia had existed, after a prolonged search they had been able to find one or two abnormal cells or myelocytes—mostly in one of them, at least, which had enabled them to recognize that a leukemia probably had existed.

In their experience the end-results of the *x*-ray treatment of leukemia were these: that, so far as known to the speaker, it was not a curative measure in the treatment of prolonged forms of the disease, the longest

case in the series cited having been eight years. During the last six years that patient had practically had a normal blood count, but had been compelled to continue the treatment, usually at intervals, because of slight increases in the number of leukocytes. Otherwise he had apparently been in good health. In one case only had the disease been arrested up to the time of the patient's death. There had been a case of lymphatic leukemia that had died, two years after treatment, of pneumonia. During those two years it was a chronic lymphatic leukemia: in that case the patient had made a complete recovery so far as the blood picture was concerned, a thing very unusual in lymphatic leukemia; because in these, more than in the myelocytic forms, there is persistence of abnormality in the leukocyte count even though the number of cells be reduced to practically normal limits. That patient, however, on the contrary returned to the normal picture, remained well for two years, and then died of pneumonia. It was a case associated with marked lesions of the gums, and perhaps it may have been a doubtful case of leukemia. It was so regarded, in a way, as a very doubtful case because of the unusually prompt results.

With the *x*-ray treatment the speaker and his associates had found what apparently Dr. Giffin had found with the radium treatment: a great many cases who exhibited a clinical improvement, with a fair degree of improvement in the condition of the blood, who insisted upon returning home and to their work when the blood count was still 20,000 or 30,000 or 40,000 and the leukemic picture still present. Some of the cases, notably two physicians, had experienced eventually better results than the cases in which the improvement in the blood picture was immediate. In these cases the change in the blood picture was delayed for some months, though the clinical improvement in the patients had been quite immediate. In these cases, eventually, a considerable improvement was made and the men returned to their practice and continued, one for at least two and the other for about three years, when there was an inevitable relapse.

All the cases cited, with exception of the fatal case mentioned, and that one enduring for eight years, had eventually relapsed. In connection therewith the speaker called attention to the fact that leukemia is occasionally, like pernicious anemia, a relapsing disease. He himself had 4 cases illustrating this now in process of publication. These cases practically spontaneously relapsed, one of them being a case that had had perhaps rather inadequate *x*-ray treatment. This patient before consulting him had asked for an examination of his blood and a hematologist reported it as normal blood. He had also been examined by another physician, who had informed the speaker that the blood was normal. Nevertheless the patient had had leukemia; a prolonged search of an hour or two discovered a myelocyte. This man has relapsed three times, each time after a slight gastro-intestinal attack. A second patient, who had been in the care of a physician in New York, with a very marked myelocytic leukemia, went

to the Adirondacks and took quite inconsiderable amounts of Fowler's solution and, in the course of a few weeks, his blood picture returned to normal. He at that time consulted the speaker, and the blood picture, despite a most careful search, with a knowledge of the preceding history and the previous findings, showed no evidence of leukemia. He since has had *x*-ray treatment and again returned to the normal picture, but subsequently relapsed and died. A third case improved without any treatment whatever; simply made a change of climate and improved by going to a part of western Massachusetts, and the change of scene (and perhaps latitude) may have contributed to that improvement. There was a return to the normal picture.

Finally, the speaker would suggest the prolongation of life by a number of years as a possible result in the treatment of leukemics. Cases in his observation had lived four, five, perhaps six years, with a maximum of eight years, which last is perhaps a greater duration of life than one would have a right to expect from the untreated disease; but whether under the best conditions a much longer lease of life might be looked for he was not prepared to say.

The clinical improvement seemed to the speaker pretty much the same, so far as his information went, as in the other method. The tendency to sharp reaction from the treatment over the spleen certainly appears to be less with the *x*-ray treatment, as he had seen it practised, than with that portrayed by Dr. Giffin. Though the former had been abandoned by the speaker and his associates, they had recently returned to *x*-ray treatment over the spleen in the late stages of the disease, after the blood picture had considerably improved, and because they had wished to avoid exhaustive and prolonged treatment over the bone, to which they had attributed the myelocytic changes that occur in the red blood cell picture in the later stages of these cases that have been subjected to long treatment.

Dr. Peabody. Our experiences in the treatment of myelogenous leukemia at the Huntington Hospital, in Boston, have been practically confirmatory of the work of Dr. Giffin. About 34 cases of myelogenous leukemia have been treated with radium, and at the present time 16 cases are under careful supervision. In general our results show a remarkably quick and complete return to normal on the part of the white count in almost every case and a great decrease in the size of the spleen. Many enormous spleens disappear wholly below the costal margin. It is, however, a very difficult problem to keep the white count low, and after a few weeks the number of leukocytes usually begins to increase. This rise in the white count has seemed to be the most important indication of more treatment. We have found it essential to follow the cases at frequent intervals, and it is our rule that they should appear for blood examinations at periods varying from one week to one month. If the patients are left to themselves they

do not usually return until they begin to have symptoms, and at this time the white count is usually 100,000 or more.

We attempted at first to keep the white count as near normal as possible, but it has seemed to me of late that the patients were functionally as well if their white count was only moderately increased. Thus we are really giving treatment if the white count is less than 20,000. As soon, however, as the white count begins to rise above 40,000 or 50,000, and as soon as the spleen begins to enlarge, a course of treatment is definitely indicated.

The most important points which are to be regarded as of prognostic importance from the point of view of the blood are the rise in the white count, a decrease in the hemoglobin or red count, and the presence of nucleated red cells or myeloblasts in the smear.

The case longest under observation came to the hospital under Dr. Ordway and has now been followed for nearly four years. During this time he has led a life which was comparatively normal, although he has been somewhat limited in his activities. One patient came to the hospital with a very high white count, improved on treatment, left the hospital, and came back again extremely sick with a white count of 100,000. He was again treated and his white count was brought to normal. At the present time he has been working for over a year, and during this period has never had a white count of over 20,000. It is, of course, impossible to say how much this result is due to a natural remission of the disease.

Dr. Foster, asking whether there is any essential difference in the action of radium and roentgen rays, both being the gamma ray, and stated his reason for asking was that during the year or year and a half past he had observed a number of cases of leukemia which had been treated by *x*-rays when the spleen alone had been exposed to the radiation. In his opinion those cases, on the whole, had shown about the same results as described in Dr. Giffin's cases exposed to radium, though no case under *x*-ray treatment had been under the speaker's observation longer than about a year and a half. One case he had seen only a short time ago had first been treated about nine or ten months previously, describing it as in his judgment about a No. 3 spleen by Dr. Giffin's scale, with a high leukocyte count, which is now quantitatively normal, although qualitatively it is not normal. His present condition is, so far as he feels, perfectly good. The spleen is just palpable. Dr. Foster thinks it quite probable, theoretically, that the same results may be obtained by *x*-rays, provided they be used in the same way that the radium is used.

Dr. Rowntree said he should like to ask Dr. Giffin if he had had any experience with acute types of leukemia, and in that connection would report one case: A girl had come in about six weeks previously, with a history of a very large spleen and a very pronounced anemia, on whom

he made a diagnosis of acute myelogenous leukemia. They had thought it best to transfuse her, and did so, bringing the blood up. They then gave her radium treatment (an exposure of 50 mgm. for about twenty-four hours). She died in the course of ten days, exhibiting no reaction. Of course the time was very short. She did not live long enough to show any effect on the size of the spleen. He asked if Dr. Giffin had used in this series anything other than radium, also whether, in his experience, with a relapse there was more difficulty in bringing the case under control in subsequent treatments, and whether he had had any experience with the intravenous injection of either radium emanation or the soluble radium salts, along with or following its use locally over the spleen. It seemed to him that it might be very well worth while to combine internal treatment with emanation or soluble salt with exposure over the spleen, inasmuch as radium is stored in the bone marrow to a very great extent. Certainly, radium intravenously increases very considerably the red count. It might, in his opinion, prove a decided improvement in this line of treatment.

Dr. Barker said some consideration should be given, from the theoretical side, to these practical studies of the radium treatment and the *x*-ray treatment of leukemia. We wondered, for a long time, whether the masses of cells of bone-marrow type, appearing at certain sites (spleen, liver, skin, etc.) outside the bone marrow really originate in the marrow and represent extramedullary metastases or whether or not they arose from primeval tissues situated in the extramedullary foci. In his opinion the evidence now is plainly in favor of the view that the anlage for leukopoietic tissue of myeloid type exists in many parts of the body, not merely in the bone marrow; though in the adult, normally, the bone marrow is the only source of supply of the cells of the blood that are of myeloid type. However, in myeloid leukemia great masses of leukopoietic tissue of myeloid type develop in the spleen, the liver, the skin, sometimes even in the lymph glands, in the lungs, and in still other organs; and the pathogenesis of these extramedullary accumulations is obscure. One must conceive, he opines, either (1) of some abnormal stimulus to the proliferation of the primitive tissue a stimulus that excites not only the tissue in the bone marrow but also the extramedullary anlagan that normally lie dormant; or (2) of the taking off of some normal inhibitory influence to the growth of this leukopoietic tissue of myeloid type in both myeloid and extramedullary situations.

In either case we deal with a tissue disease rather than with an organ disease; in other words, myeloid leukemia is not simply a disease of the bone marrow or a disease of the spleen, but it is a disease in which leukopoietic tissue of myeloid type all over the body undergoes proliferation. An interesting question from the theoretical side is, How can radium or

x-rays applied to the spleen alone or to the bones alone bring to a stand-still a proliferation process that involves a tissue of such wide distribution? Is it possible that in applying radium or *x*-rays, say to the spleen, we are in reality applying an agent that exerts a more widespread effect than we had thought, influencing cells not only in the spleen but in a much wider area at the same time? It would seem scarcely possible that the radioactivity itself can be so diffuse when locally applied. It would seem more likely that the destruction of cells in the spleen or the bone marrow through the local application of *x*-rays or of radium resulted in the setting free of certain substances that, in turn, affect the whole leukopoietic tissue of myeloid type everywhere in the body probably by inhibiting the growth. Another possible explanation of the favorable effect of raying locally would, in the speaker's opinion, be that the destruction of a certain number of cells of this leukopoietic tissue of myeloid type in the spleen or in the bone marrow by diminishing the total amount of this tissue could permit the normal inhibitory processes over the body to be sufficient to control the growth of the tissue remaining undestroyed. Just as when we operate on the thyroid gland in Graves's disease we do not remove all of the hyperplastic tissue, but very often the patients get well. They often begin to get well right away, probably, perhaps, because when the excess of tissue is removed the body is able to control what remains. That is the view it would seem worth while to consider.

In reducing the white count in the blood in leukemia we affect only a symptom merely, rather than the disease itself. If we are ever able satisfactorily to control leukemia it would seem that we must acquire a better knowledge of the etiology and pathogenesis of the malady. We must face the fact that it is a tissue disease rather than an organ disease, and we must try to find out the conditions that favor, on the one hand, and that inhibit, on the other hand, the proliferation of this tissue.

Dr. Libman said in regard to the suggestion by Dr. Barker, that there exists a leukolytic activity of the serum in at least certain cases of leukemia, and there is evidence in the literature that this leukolytic activity can be developed or increased by action of the roentgen rays. Interesting in this connection are the observations of Dr. Ottenberg, who found that in some cases of leukemia the polynuclear cells transfused from a donor into patients with leukemia were gone after twenty-four hours. In cases of leukemia one occasionally observes a sharp temperature rise with a sudden drop in the number of leukocytes in the blood. This indicates the occurrence of leukolytic crises.

One occasionally sees very remarkable changes in the blood in cases of leukemia after transfusion. Dr. Harold Neuhof, of New York, reports a case with a blood count of 200,000 cells in which within a month after transfusion the number of cells was normal and the number remained

about the normal figure during the rest of the year after the transfusion, the patient dying of a condition that was diagnosed as mycosis fungoides. The most rapid effect that Dr. Libman has seen in the treatment of leukemia was observed in a case treated at the Mount Sinai Hospital by Dr. Richard Weil. After one intensive application of radium the spleen in less than within a week decreased to almost normal size and the blood count dropped almost to the normal figure, the blood, however, not being normal in its composition.

Dr. Rosenthal said: Recently we have observed one case in whom radium treatment had evidently been carried on too vigorously. In this patient the white blood cells dropped from 160,000 to 1000 per cubic millimeter. At the same time the red blood cells diminished from 3,000,000 to 600,000 per cubic millimeter and the hemoglobin from 50 to 16 per cent. It was only after many weeks of therapy, by means of transfusions and forced diet, that the red blood cells were brought to 4,500,000 per cubic millimeter, and that the patient regained his strength. It would appear from this experience that treatment by radium in cases of myelocytic leukemia must be employed with a certain degree of caution.

Dr. Solis Cohen said he had had the opportunity to observe both radium treatment and *x*-ray treatment in various forms of leukemia, the difference seeming to be that the radium treatment is more prompt and exposes the patient to less danger of severe constitutional reaction. As to the duration of the improvement that will occur it is hard to say. Under *x*-ray treatment he had, like Dr. Stengel, seen cases which had lasted from four to seven, and, in one case, to ten years. That was a very curious case. The man had walked into the speaker's office and declared he had leukemia. His spleen was of the type described by Dr. Giffin as "No. 4." The white cell count, however, was only 50,000, but the patient said that at the beginning of his affection, six years before, his leukocyte count had been something like 200,000. He had been under treatment in various European and American cities. He is in the employ of an engineering concern, which sent him from place to place. He might live in one place for a certain number of years; in another for months or weeks only. He was under Dr. Solis Cohen's care for about two years, and, so far as his spleen was concerned, remained in a stationary condition. The leukocytes varied from time to time, but the changes were of minor importance. All of this time he was able to work very hard in his profession. He had been sent from Philadelphia to some point in the West, and recent advices announced his death, about ten years, so far as could be ascertained, from the recognition of the disease. The speaker knew not whether his treatment of this patient had produced any effect, but at all events he had been under observation. One part of the treatment had been consistent throughout

the patient's migrations, namely, keeping the intestinal canal free from undue sepsis, keeping the mouth in good condition, and keeping up the administration of arsenic. X-ray treatment had been intermittent—or rather remittent. In the speaker's experience the combination of radiation (whether by x-rays or radium) with arsenic, also in some cases the expedient suggested by Morton, of New York, the administration of fluorescing substances during the time that the radiation treatment is continued, had seemed to be followed with the greatest prolongation of life, and with the greatest amelioration of symptoms; but what Dr. Barker had brought out must not be forgotten, that we are here dealing with a pathological process the nature whereof we do not clearly know and the etiology whereof we know not at all. The speaker's guess at its etiology is infection, and it may be that the radiation has something to do with inhibiting or destroying the infective agent as well as the infected cells; but this is a guess about a guess. Another useful expedient seems to be the internal administration of recent radium emanation water; that is, radium emanation dissolved in water and swallowed at frequent intervals in as recent a stage as possible.

Dr. Capps thought it unquestionable that both the x-ray and radium treatments destroy the characteristic cells in leukemia and produce some sort of chemical substance having, in turn, a destructive action on these cells. This had been shown by the work of Heineke and some of his associates, and had previously been reported by Dr. Smith and the speaker before this Association. In the latter instance a case of leukemia of the lymphatic type had been thoroughly treated by x-rays, rendered almost free of lymphoid cells, and the spleen reduced to normal size. The patient had thus been "clinically cured," and remained so for a period of several months. The speaker and his associate had drawn blood from this patient, defibrinated it, injected the serum into another patient with an untreated lymphatic leukemia, and succeeded in reducing the white cells in twenty-four hours from 170,000 to 100,000 in the first experiment; in the second experiment from 165,000 to 120,000; in the third experiment from 320,000 to 220,000. While none of these effects were lasting, they had shown the immediate effect of the serum from the x-rayed patient on the blood of the untreated patient, and had shown that some leukocytic substance had been produced in this serum as the result of exposure to x-rays; also, that this substance was more or less selective. Thus, in the lymphatic leukemia, they had found that the lymphoid cells were the first attacked. Similar experiments with myelocytic leukemia gave evidence of a selective destructive action upon the myelocytes and myeloblasts.

Dr. Giffin (closing) stated that he wished to emphasize the fact that the results of radium treatment were quite consistent. In every case there was some fall in the leukocytosis and some reduction of the spleen. He

said he was glad to hear Dr. Peabody say that it is better to maintain the patient's good general condition than to endeavor to reduce the leukocyte count to a very low point. He recommended resort to transfusions upon the development of severe anemia. In the series of cases discussed, arsenic had not been used until after a definite effect had been obtained with radium. No patients with acute leukemia had been treated and very few patients with chronic leukemia during relapse. While there had been some favorable results in relapses, it could not be definitely stated how they compared with the original effect. The use of intravenous emanations had been considered, but it was not thought wise to give this form of treatment a trial at present.

DIAGNOSTIC SIGNS FROM THE SCALENI, INTERCOSTAL MUSCLES, AND THE DIAPHRAGM IN LUNG VENTILATION

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During the past few years respiration has come in for a bountiful share of physiological and clinical research, but all of the research has been directed toward gaining some understanding of the exquisitely nicely balanced relations of excitatory and inhibitory influences which modify the rate, rhythm, and amplitude of respiration.

Chemistry of the blood in its relation to respiratory function also has been the subject of much research, but the simpler problem of lung ventilation and its clinical analysis has been neglected. In every clinical examination we should form some definite idea about the volume, density, and extensibility of the upper and lower lobes of the lungs. An understanding of these three physical attributes is the goal toward which most methods of physical examination of the lungs have been directed. Density of the lung, with some adventitious signs, has occupied the attention of clinicians much more than volume and extensibility of the lung.

To form a clear estimate of volume and extensibility of the lung we must have a clear conception of the physiological mechanism by which lung ventilation is accomplished. In every case we must estimate:

1. The inspiratory enlargement of the thoracic cage in three dimensions.

2. The relative height of that portion of the diaphragm underlying the heart and the height of the two leaves of the diaphragm underlying the lung.

3. The share of the scaleni in the movement of the upper four ribs.

4. The share of the intercostal muscles in the movements of all the ribs from the second rib to the twelfth.

5. Besides the above-named diagnostic points we must also differentiate the evidences of diaphragmatic activation from the evidences of diaphragmatic excursions.

In other words, to have a clear conception of the ventilatory function of the lung we must in every case point out the evidences of the functions of the scaleni, the intercostal muscles, and the diaphragm.

Briefly stated, the function of the scalenus muscle is solely to form a point of fixation in the first rib from which the second, third, and fourth ribs are elevated. The increase of the antero-posterior and transverse diameters of the thorax is accomplished entirely by the intercostal muscles. The increase of the longitudinal diameter of the thorax is due solely to the descent of the diaphragm.

These are the simpler facts, but the diagnostic problems which arise in clinical work require us to recognize what modifications of the respiratory excursion of the thorax betray a paralysis of the scaleni muscles or paralysis of the intercostal muscles or paralysis of the diaphragm.

We must also differentiate between evidences of activation of the diaphragm and evidences of excursion of the diaphragm.

I shall also show how we can recognize moderate depression of the middle portion of the central tendon of the diaphragm as occurs in enlargement of the right ventricle of the heart and with small amounts of fluid in the pericardial sac. We can also recognize a depression of the left lateral portion of the central tendon due to enlargement of the left ventricle when the right ventricle is not enlarged.

By studying the inspiratory excursions of the costal margins we can recognize various degrees of depression of the muscular leaves of the diaphragm, namely, when the under surface of the leaf is convex, as in very large pleural effusions, when the leaf approximates a plane, as in moderate effusions, and when the

convexity of the upper surface of the leaf is increased, as occurs in hepatic enlargement and accumulations of pus or fluid between the diaphragm and liver.

This can be learned by studying the inspiratory excursion of the median and lateral portions of the costal margins. This is all possible because the movement of the costal margins expresses very accurately the balance between the intercostal muscles and diaphragm in their contest for mastery of the costal margins.

The median portions of the diaphragm are much less arched than the lateral portions, consequently much less depression of the median portion of the diaphragm is necessary to modify the normal excursion of the internal portion of the costal border than is required to modify the normal excursion of the external portion of the costal borders.

With this general statement of the argument I shall proceed to illustrate the specific points by a number of clinical and experimental data.

Ventilation of the Upper Lobes of the Lung. Long ago the observation was made that the infraclavicular region exhibited an "undulatory movement during inspiration." This undulatory movement is due to the varying size of the upper five ribs. The lengths of the upper five ribs increase in size from the first to the fifth.

During inspiration the first rib is not elevated, but the second, third, fourth, and fifth ribs are elevated by the so-called bucket-handle movement. The maximum movement of a rib will be in that portion farthest from the axis of rotation, consequently the external portion of the rib will move through a greater distance than the parts nearer the axis of rotation.

The distance through which a rib will move in response to an inspiratory activation of the intercostal muscles will be limited by the extensibility of the underlying lung. The movements of the upper five ribs very faithfully mirror the movement of the underlying lung, consequently any disease which will impair the extensibility of the lung will modify the normal undulatory movement of the upper five ribs.

Any disease of the pleura, occlusion of a bronchus, or inflamma-

tory process in a lung will diminish its extensibility. Extensibility is the first attribute which is modified in any inflammation of the lung. This diminution of extensibility can be detected before any increase of density is demonstrable. Consequently the sign bears a very important significance in the early recognition of pulmonary tuberculosis of the upper lobes.

The undulatory movement varies in different normal persons just as the pitch of the percussion note varies. The more flexible the cartilage of the ribs the more active the bucket-handle movement will be.

This phenomenon is observed best by the examiner when standing at the right of the recumbent patient. The examiner should use his left hand. Place the tip of the ring finger on the second rib at the midclavicular line, the tip of the middle finger on the third rib midway between the midclavicular and the anterior axillary line, and the tip of the index finger on the fourth rib in the anterior axillary line. The patient is then instructed to make a moderately rapid and moderately deep inspiratory movement. The finger on the third rib will be observed to move farther than the finger on the second rib, and the finger on the fourth rib will move farther than the finger on the third rib. The movement in each rib from above downward succeeds and exceeds that in the rib just above.

Should there be only a moderate impairment or diminution of ventilation in the upper lobe the three ribs will move in unison and move the same distance, so the undulatory phenomenon will be lost, although all the ribs involved may exhibit a considerable excursion during inspiration. By comparing the undulatory movement on the two sides we have a very delicate method of comparing the amount of ventilation in the upper portions of the upper lobes.

Anything which will slightly diminish the amount of ventilation on one side or the other will show a disparity in the undulatory movement between the two sides. We find this true in any disease which will encroach on the air spaces or invade the interstitial tissue of the lung or occlude a bronchus or displace a part of the lung, as occurs in mediastinal tumor. The undulatory movement will be diminished on the left side when the heart is enlarged in an

upward direction or when the pericardial sac is distended, and also when the pleura is thickened so its extensibility is diminished.

Localized emphysema of an upper lobe of the lung will reveal a diminished undulatory movement because the ribs are in a partial inspiratory phase at the beginning of an inspiration.

If the sign is taken for exactly what it amounts to, namely, a diminished ventilatory volume of the upper part of the upper lobe, it will be of great diagnostic service. Further diagnostic signs must aid in determining what has contributed to a localized diminution of ventilatory function of the lung.

The greatest practical use of this sign rests on the fact that in all diseases of the lung a diminution of extensibility is demonstrable earlier than changes in volume or density of the lung can be demonstrated. Certainly in the early or latent periods of pulmonary tuberculosis, diminished extensibility can be demonstrated when no evidences of alteration in density or volume of the lung can be elicited, and also when all adventitious signs are absent.

An exact study of the comparative extensibility of the upper lobes should constitute a part of routine clinical examinations. In our experience at Lakeside Hospital this procedure has been the source of many diagnostic successes, and it has also aroused many interesting diagnostic problems which otherwise would have escaped our observation.

Role of the Scaleni Muscles. The following case gave rise to a study of the differentiation between the role of the scaleni and intercostal muscles in respiratory excursion of the upper five ribs.

A child about two years old, in the children's ward at Lakeside Hospital, was admitted with well-advanced signs of a congenital muscular disease. There was absolute paralysis of all the muscles which contribute to movements of the head on the spine. The respiratory excursion of the thorax presented a very unusual picture. During inspiration the manubrium with the first three ribs was drawn strongly downward and inward, the fourth ribs remained stationary, but the fifth ribs and those below moved upward to an unusual extent. The subcostal angle widened much more than in normal children. Both hypochondria moved outward much more than in normal cases. There was, however, no inspiratory

retraction of the suprasternal notch or of the supraclavicular spaces.

The exaggerated spreading of the hypochondria and descent of the first three ribs and manubrium with each inspiration presented a very unusual and perplexing problem for analysis. The question which arose was whether the entire picture was due solely to paralysis of the scaleni muscles or if the upper intercostal muscles also shared in the progressive muscular disease.

Experiment A. Under ether anesthesia the three scaleni muscles of the right side of a dog were exposed and cut immediately above the first rib. The first, second, and third ribs of the right side were drawn downward with each inspiration. The fourth rib remained stationary and the fifth rib with all those below it moved upward as in a normal animal. On the left side the first rib remained stationary, but the second, third, fourth, and fifth ribs exhibited the usual normal undulatory movement above described. When the scaleni of the left side were cut, as those of the right side were cut in the beginning of the experiment, the same phenomena of respiratory excursion were produced on the left side. The respiratory excursion of the dog's thorax was identically like that of the child's thorax.

Experiment B. A young dog about one and a half years old, was given morphin and ether anesthesia. The sternomastoid and scapula of the right side with all its muscular attachments were removed, so there were only the scaleni, intercostal muscles, and diaphragm left. The respiratory excursion of the entire thorax was unchanged. Then the scaleni were cut on the right side and the same changes in respiratory excursion were plainly seen on the right side as described in experiment A. The scaleni of the left side were then severed and the same descent of the upper three ribs with fixation of the fourth rib and upward movement of the fifth rib with those below occurred as in the former experiment.

If the upper end of the sternum was grasped with forceps and held in position so the manubrium could not descend during an inspiratory movement there was a return to the normal inspiratory evolution of the upper ribs. When the manubrium was released the picture of the child with paralysis of the scaleni was again reproduced.

Experiment C. Under morphin and ether anesthesia the spinal cord of a dog was severed at the sixth cervical segment. The scaleni and diaphragm were thus preserved, but all the intercostal muscles were paralyzed. There was no inspiratory descent of the upper ribs or manubrium, but with each inspiratory descent of the diaphragm the upper lateral portions of the thorax were retracted. There was no elevation of the first ribs during inspiration.

Experiment D. The following experiment shows how the structure of the bony thorax may greatly modify the phenomena thus far described. A well-grown young dog, who still had his puppy teeth, was given morphin and ether anesthesia for the purpose of making other observations, but incidentally the scaleni muscles on both sides were exposed and severed. Instead of the phenomena observed in our former experiments the first ribs were drawn downward with each inspiration, the second ribs were drawn in an upward direction, so the second ribs did actually override the first ribs to a slight degree. The manubrium was not drawn downward. The second, third, and fourth ribs exhibited the normal undulatory movement seen under normal conditions.

These experiments suffice to show that the scaleni do not contribute to the inspiratory elevation of any of the ribs. The scaleni simply supply an anchorage for the first ribs only, and the evolution of the ribs during inspiration from the second downward is accomplished entirely by the intercostal muscles. I have had the opportunity of seeing only the one clinical case of paralysis of the scaleni, so from our experimental experience on dogs we may expect to find the inspiratory movements of the upper four ribs to differ in patients just as occurred in our dogs.

There may be an inspiratory descent in a caudal direct on of only the first ribs with a normal evolution of all the ribs from the second rib downward, or there may be an inspiratory descent of the upper three ribs and manubrium with fixation of the fourth rib and elevation of all the ribs below the fourth. This will depend on the mobility of the upper ribs and the manubrium. If the upper ribs and manubrium form a comparatively rigid structure, then only the first rib will be drawn downward with each inspiration

if the scaleni are paralyzed; but if the manubrium and upper ribs are quite flexible, as in the child described, then paralysis of the scaleni will cause the inspiratory excursion of the thorax to present a very striking picture of increased spreading of the hypochondria and retraction in a caudal direction of the manubrium and upper three ribs.

The Diaphragm and Intercostal Muscles. The diaphragm and intercostal muscles are antagonists in two ways: The intercostals serve to increase the anteroposterior and transverse diameters of the thorax and the diaphragm serves to increase the longitudinal diameter of the thorax. Activation of the intercostal muscles will tend to diminish the longitudinal diameter of the thorax unless resisted by the diaphragm, and activation with excursion of the diaphragm will cause a diminution in the other two dimensions of the thorax with narrowing of the subcostal angle unless resisted by the intercostal muscles. Much confusion has been introduced into this subject by failure to differentiate the evidences of diaphragmatic activation from the evidences of diaphragmatic excursion and also the failure to recognize the significance of the arch of the diaphragm as a whole, and the significance of varying curves of different parts of the diaphragm has led to much confusion and misinterpretation of the respiratory movements of the costal margins.

The modern interpretation of the function of the intercostal muscles and the diaphragm has hitherto rested on the work of Duchenne, of Boulogne, which was published in 1853 under the title of *Recherches Electrophysiologiques et Therapeutiques sur la Diaphragme.* A critical review of Duchenne's work is very interesting in the light of more modern writers and the author's observations on patients and animals.

Duchenne proposed the following problems in his work:

"Does the diaphragm in its contraction constrict the lower part of the thorax by drawing the lower ribs downward, or, on the contrary, does the diaphragm increase the transverse and anteroposterior diameters of the lower half of the thorax by lifting the diaphragmatic ribs upward and outward?"

"Does there exist a difference between the physiological action

of the diaphragm in its relation with the abdominal viscera and the action of the diaphragm when it is deprived of its visceral relations?"

"Finally, what is the mechanism of the action of the diaphragm on the thoracic walls?"

Then follows an interesting historical résumé of the study of the diaphragm which shows what difficulty attended the interpretation of the function of the diaphragm in conjunction with the spread of the hypochondria and widening of the subcostal angle.

"The anatomists of antiquity recognized only one muscle of inspiration and ascribed to the diaphragm the duty of carrying the ribs upward and outward. But Galen recognized other muscles of respiration and ascribed to the diaphragm only the function of lifting and spreading the lower ribs. Vesalius, however, questioned this. He interpreted the action of the diaphragm as resulting in an elevation of the diaphragm. Columbus (his pupil) denied this and said the diaphragm was depressed by inspiration, but that the diaphragm was relaxed during inspiration. Activation of the diaphragm constricted the lower ribs, but owing to relaxation during inspiration the diaphragmatic ribs were permitted to spread."

Borelli, the physicist, cited by Duchenne, was the first to claim that the diaphragm contracted during inspiration and increased the longitudinal diameter of the thorax, and by virtue of its attachments to the ribs must necessarily by its action constrict the lower part of the thorax. Borelli claimed the diaphragm could not act independently of the intercostal muscles.

The idea of Galen was forgotten until 1833, when Magendie again took up the idea and said that the spreading of the lower thorax from diaphragmatic contraction and descent was due to the resistance of the viscera under the vault of the diaphragm, and as the ribs were readily moved the compression of the viscera caused increase in the transverse diameter of the upper abdomen and thus pushed the ribs outward. Duchenne says Magendie never supported his idea, however, by any animal experiment.

In 1843 Beau and Maissiat undertook to establish the doctrine of Galen by experimental methods. They cut the lower six intercostal structures through from the sternum to the vertebræ on

both sides after cutting the scaleni and all other thoracic muscles which might share in respiratory excursion. Only the upper intercostals and the diaphragm were left and the lungs were collapsed. Beau and Maissiat observed that under the conditions the diaphragmatic ribs were elevated and the base of the thorax was widened. When the diaphragm was hastily cut away the base of the thorax was immobilized. They confirmed Galen's observation but said nothing about the role of the viscera underneath the diaphragm contributing to the spread of the lower thorax during inspiration. M. T. de Brou (*Gaz. Méd.*, 1843, p. 344) repeated the experiments of Beau and Maissiat and came to just the opposite conclusion.

As we will see later the differing results of these observers was due merely to a difference in the vaults of the diaphragms of the dogs used by the experimenters. De Brou evidently used a dog which had less convexity to his diaphragm than had the dog which was used by Beau and Maissiat. Under the experimental conditions a dog with a long thorax and high arch to his diaphragm would show an inspiratory widening of the subcostal angle, whereas a dog with a shorter thorax with less convexity to his diaphragm would show an inspiratory narrowing of the subcostal angle. The reason for this will be discussed later.

Up to the time of Duchenne great doubt existed as to whether or not the diaphragm played any role in inspiratory widening of the base of the thorax. Since Duchenne's experiments, however, widening of the subcostal angle has been ascribed in part to diaphragmatic action. It is this error which has caused so much confusion and misinterpretation of the respiratory movements of the costal borders.

Duchenne applied electrodes over the phrenic nerve in front of the scalenus anticus and observed protrusion of the epigastrium and an outward movement of the costal margin on the affected side. This is an observation which is unreliable because one could not be sure that the intercostals of the affected side were not also activated.

Duchenne then exposed the phrenic nerve of a dog and stimulated the nerve with an electric current, and observed the same movements of the epigastrium and costal margin. This is contrary

to the results which I procured by stimulating the exposed phrenic nerves of dogs. We must, however, take into account that Duchenne's observations were made on dogs with unopened abdomens, whereas my observations were made on dogs with abdomens opened so I could see the movements of the diaphragm. In my experiments the costal margins were drawn violently toward the median line when the exposed phrenic nerves were stimulated by an electric current.

Duchenne repeated his experiments on both horses and dogs and got the same results, but in both horses and dogs phrenic activation caused retraction of the hypochondria and narrowing of the subcostal angle, when the abdomens were opened and all the viscera removed from the upper abdomen. Duchenne says[1] that such diaphragmatic activation has an expiratory result. We will see later that Duchenne's animals would have shown a narrowing of the subcostal angle from isolated phrenic activation had the abdominal wall been opened so as to allow the entrance and exit of air during respiration. It was not necessary to disturb the abdominal viscera to change the direction in which the costal margins moved during phrenic contraction.

In a former communication[2] the author described several experiments in which it was clearly proved that when the diaphragm was activated by electric stimulation the costal margins were violently drawn toward the median line. All these experiments, however, were done with the abdomen opened so the movements of the diaphragm were plainly visible from its lower surface.

In the meantime a patient suffering from fracture of the sixth cervical vertebra was observed in whom there was complete motor paralysis of all muscles supplied below the sixth cervical segment. The scaleni and diaphragm were preserved, but all the intercostal muscles were paralyzed. During inspiration the first ribs were stationary and the hypochondria were retracted with each inspiration. The subcostal angle was much narrowed with each inspiration. The entire costal margins on both sides were drawn toward the median line with each contraction of the diaphragm.

[1] Arch. Int. Med., 1913, xii, 214.
[2] Ibid., xii, 214–224.

Experiment E. A dog of the setter type was anesthetized with ether and then the cervical cord was sectioned at the sixth segment. To our surprise we found a respiratory movement of the thorax which was quite different from what we expected to find in view of our former experiments and clinical observations. The first ribs were stationary. There was only inspiratory retraction of the costal and intercostal spaces in the upper thorax, but to our surprise in the lower thorax there was a very different picture. From the ninth to the twelfth ribs inclusively there was an outward movement with distinct widening of the subcostal angle during inspiration. The character of the movement, however, was not such as we see when the intercostal muscles are active. The outward movement of the lower ribs was evidently a passive and not an active movement. The movement was quite like that observed by Beau and Maissait and by Duchenne in their animal experiments.

An incision was then made in the linea alba, so the peritoneal cavity was opened and then a reverse movement in the lower ribs occurred. During inspiration the entire costal margins and hypochondria of both sides were drawn toward the median line. The abdominal wound was then clamped and the former inspiratory widening of the subcostal angle occurred. This observation was repeated a number of times until it was clearly apparent that removal of the viscera was not necessary to convert the inspiratory widening of the subcostal angle to inspiratory narrowing of the angle. When the abdominal wound was closed we evidently had the same physical conditions as before the incision was made.

The dog's diaphragm is more convex than the human diaphragm. The dog has thirteen ribs, and in some breeds of dogs, such as the setter, the thorax is particularly long, with a very acute subcostal angle. Such a conformation gives a high dome to the diaphragm, so that when the intercostal muscles are paralyzed the subcostal angle widens during inspiration because there is such a great disparity between the resultant line of traction of the diaphragm and the anatomical line of the diaphragm. The resultant line of traction is a straight line drawn from the central tendon to the costal margins where the diaphragm is inserted. When the abdomen is

closed the respiratory descent of the diaphragm is attended with an increase in intra-abdominal pressure which is transmitted equally in all directions. If the lateral pressure in the abdominal cavity produced by descent of the diaphragm exceeds traction on the costal margins, then the hypochondria will spread during inspiration, although the intercostal muscles may be paralyzed. When there is an opening in the epigastrium, then descent of the diaphragm simply displaces the air and does not increase the intra-abdominal pressure, consequently there is no pressure to counterbalance the traction on the costal margins, and the entire costal margin is drawn toward the median line. It will be observed, also, that when the intercostal muscles were paralyzed in this particular dog only the ninth, tenth, eleventh, and twelfth ribs moved outward, the sixth, seventh, and eighth ribs were stationary. This was due to the varying curve of the diaphragm in its different parts. The anterolateral portion of the diaphragm has less convexity than those fibers in the lateral portion which are inserted in the lower ribs. Consequently the less disparity there is between the curve of the fibers and the straight line of resultant traction the more advantage will traction acquire over any force which tends to move the costal ends or ribs away from the median line.

This was proved by repeating the experiment on a dog of the bulldog type which has a shorter thorax and less acute subcostal angle than the dog used in the experiment just described. When the intercostal muscles were paralyzed by section of the dorsal spinal cord at the fourth dorsal segment all the intercostal muscles below this level were paralyzed, but unlike the previous experiment the entire costal margins on both sides were drawn toward the median line. The movement of the costal margins was unchanged by opening the abdomen. In this manner I believe we can account for the time-honored experiments of Duchenne and also for the differing results obtained by his predecessors. Duchenne evidently used dogs with a high arch to the diaphragm and so did Beau and Maissiat, but de Brou, in his experiment, employed a dog with less convexity of the diaphragm and observed both costal margins drawn toward the median line during inspiration. Thus it seems that finally we have a satisfactory explanation for the conflicting results obtained

by different experimenters who have studied the function of the diaphragm.

I have never seen an instance of paralysis of the intercostal muscles in man which was attended with inspiratory widening of the subcostal angle and spreading of the hypochondria. This is due to the fact that the dome of the diaphragm is not sufficiently arched to permit the inspiratory increase of pressure within the abdomen to exceed the diaphragmatic traction on the costal borders during inspiration.

The significance of the arch of the diaphragm for inspiratory movements of the costal margins was fully discussed in a publication[1] by the author four years ago. Since that time there has been gathered much confirmatory evidence.

I have had three experiences which prove the correctness of the idea that the true explanation lies in the disparity between the resultant line of traction and the curve of the diaphragm and not in the height of the diaphragm. If the curve of the diaphragm is responsible for the outward movement of the costal borders during inspiration then it is obvious that the costal margin should diverge from the median line when the diaphragm is convex on its under surface as well as when it is convex on its upper surface.

This was observed to be a fact in two cases of thoracic empyema of the left side in which the normal spleen was displaced below the costal border by the downward displacement of the diaphragm. In both cases there was inspiratory divergence from the median line by the left costal border. One quart of pus was then aspirated and then the left costal margin was drawn toward the median line during inspiration. Later two more quarts of pus were aspirated, whereupon the left costal margin diverged from the median line. When the line of traction and the plane of the diaphragm coincided, *i. e.*, when the diaphragm was arched neither upward nor downward, then the acting diaphragm gained the mastery over the costal border against the antagonists, namely, the intercostal muscles. When the diaphragm was arched either upward or downward then there was sufficient disparity between the resultant line

[1] Arch. Int. Med., August, 1913, xii, 214–244.

of traction of the diaphragm and the curved surface of the diaphragm, so that the diaphragm's antagonists (the intercostal muscles) gained the mastery of the costal margin and moved it away from the median line during inspiration.

These cases also prove the incorrectness of the idea of the piston descent of the diaphragm during inspiration being the cause of the inspiratory spread of the hypochondria. When the left diaphragm was convex on its under surface its contraction caused a lengthening of the abdominal cavity instead of the normal shortening, so there could have been no inspiratory increase of the intra-abdominal pressure from activation of the left diaphragm. In spite of this fact the costal margin moved away from the median line during inspiration just as when the diaphragm was convex on its upper surface.

There are other reasons to prove that in man the piston-like descent of the diaphragm is not a factor in the inspiratory widening of the subcostal angle. The curves of different groups of fibers in the diaphragm vary greatly. There is much less curving of the fibers which pass from the central tendon of the diaphragm to the costal margin near the median line than there is in those fibers which pass from the central tendon to the costal border in the axillary line. We see the line of the diaphragm at its sternal portion more nearly approaches a straight line than at any other part. The anterolateral part of the diaphragm requires less depression to give this part of the diaphragm a horizontal position than is required to accomplish the same for parts occupying a more lateral position. The anterolateral part of the diaphragm has a slight curve to its fibers from origin to insertion; it is very near the critical position, so that very slight depression is required to give this portion of the diaphragm the mastery over that portion of the costal margin where it is inserted.

When the heart or pericardial sac is enlarged to a moderate degree that part of the costal margin from the median line to the ninth costal cartilage will be drawn toward the median line during inspiration; but beyond this median half of the costal margin the inspiratory movement is in a lateral direction. On several cases I have observed the reverse of this when the posterolateral portion

of the pleural sinus was filled with fluid. The subcostal angle widened during inspiration, but the lower and lateral portion of the costal border was retracted.

When the entire lung is emphysematous to a sufficient degree to cause retraction of any portion of the costal margin the entire margin is retracted. Under these conditions there is inspiratory narrowing of the subcostal angle and inspiratory retraction of the whole of both costal borders.

In my former communication the importance of this sign was pointed out as the only method of estimating the higher degrees of emphysema. Moderate emphysema of the pulmonary borders may fill the pleural sinuses so that lung resonance will descend to the bottom of the pleural sinus in the anterior, lateral, and posterior lines; but if the great body of the lung is not emphysematous there will be no inspiratory narrowing of the subcostal angle. For example, a patient with chronic bronchitis and emphysema will have the lower borders of the lungs at the eighth, tenth and eleventh ribs respectively in the anterior, axillary, and scapular lines and have no respiratory discomfort or inspiratory retraction of any part of the costal margins; on the following day the man may have cyanosis and dyspnea with a rise of 2 per cent. in the CO_2 concentration of the alveolar air. The percussion borders of the lungs are unchanged but the body of the lung is much larger, and the only physical sign of this enlargement will be inspiratory narrowing of the subcostal angle and inspiratory retraction of the entire costal margin of both sides.

Furthermore, this differentiation between depression of the anterolateral portion alone of the diaphragm from depression of the entire diaphragm is important in estimating the pulmonary and cardiac sources of air hunger. It is not at all uncommon to see patients with moderate emphysema whose hearts are enlarged. The percussion borders of the lung may reach to the bottom of the pleural sinuses, but if there is only inspiratory narrowing of the subcostal angle, and the costal margins below the ninth costal cartilages move laterally during inspiration, then the patient's air hunger is not due to emphysema, for when air hunger from emphysema exists there will be not only inspiratory narrowing of the sub-

costal angle but there will be inspiratory retraction of the entire costal margin.

A careful study of the subcostal angle is also important to determine the symmetry or asymmetry of movement of the two costal margins in their upper or median parts.

If the patient should have enlargement of the left ventricle alone, as in cases of arterial and aortic valve disease, then the median portion of the left costal margin will be retracted or move less in an outward direction during inspiration than the symmetrical part on the right side will move outward during inspiration.

In cases of mitral stenosis, myocardial disease, and enlargement of the pericardial sac there will be symmetrical narrowing or constraint of the subcostal angle during inspiration if the anterolateral portion of the diaphragm is depressed beyond the critical point. These points are all specifically mentioned because the writer has found an analysis of the respiratory movements of the subcostal angle and costal borders has been of much service in arriving at an estimate of the relative enlargement of the two sides of the heart, enlargement of the pericardial sac, and enlargement of the entire body of the lungs.

In a routine examination it is important to determine the symmetry or asymmetry of movement in the subcostal angle and lower costal margins and the relation of their movements to the median line. When the arch of the diaphragm is accentuated, as in cases of hepatic enlargement or subphrenic accumulations of pus or serum, then the outward movement of the costal border on the affected side is increased. Accentuation[1] of the diaphragmatic arch and fixation of the diaphragm to the thoracic wall were discussed in a former article, so I shall refrain from discussing this phase of diaphragmatic action any further than to describe a single experience of recent date in which the balance between the intercostal muscles and diaphragm was clearly illustrated. The patient had an acute suppurative pylephlebitis which produced a moderate enlargement of the liver in an upward direction. The patient had violent and protracted hiccough in which the diaphragm and inter-

[1] Loc. cit.

costals were both activated. On the left side the costal margin was drawn toward the median line with each hiccough, on the right side the costal margin moved away from the median line with each hiccough. At the autopsy nothing was found to account for this asymmetry of movement of the costal margins excepting a very moderate enlargement of the liver in an upward direction.

In studying the respiratory movements of the base of the thorax we must differentiate between evidences of phrenic activation and phrenic excursion.

The Litten diaphragm phenomenon is an evidence of phrenic excursion and is a supraphrenic phenomenon which is present only under normal conditions or conditions which approximate the normal. The sign is not present under abnormal conditions.

The direction of movement and comparative movements of the median and lateral portions of the costal margins on the two sides give us valuable information on activation of the diaphragm and the position of its median and lateral parts. The direction in which any portion of the costal margin may move is determined by the resultant of two forces: One is the expression of the action of the intercostal muscles which always widens the subcostal angle and spreads the hypochondria, the other force originates in activation of the diaphragm and always draws the costal margin toward the median line. When the resultant of these two forces causes narrowing of the subcostal angle the subcardial or median portion of the diaphragm is less convex than normal. When the entire costal margin is drawn toward the median line the entire phrenic leaf has lost a large part of its convexity. The movement of the costal margins has nothing to do with excursion of the diaphragm, it is merely the resultant of activation of the intercostal muscles and activation of the diaphragm. The only subphrenic sign of phrenic excursion is protrusion of the epigastrium and lateral portions of the abdomen.

The significance of the slight arch of the anterolateral portions of the diaphragm is illustrated very nicely in cases of acute cardiac dilatation due to myocardial incompetence from arterial sclerosis. It is a common experience to see these patients brought to the hospital with dilatation of both sides of the heart. During this period

there will be symmetrical inspiratory narrowing of the subcostal angle, but the lower and lateral portions of the costal margins move away from the median line during inspiration. As the heart recovers from its acute dilatation the upper and inner half of the right costal margin will resume its outward movement during inspiration, but the left side of the subcostal angle will be restrained in its outward movement or may continue to move toward the median line during inspiration. This is, of course, due to the fact that the left ventricle is permanently enlarged and depresses the left sternocostal portion of the diaphragm. The symmetry and asymmetry of movement of the two sides of the subcostal angle and the lower and outer halves of the costal margins give much valuable information concerning the total volume of the lungs and form and size of the heart and heart sac. Furthermore, an exact analysis of the respiratory movement of each part of the thoracic cage is essential to form an adequate estimate of the ventilatory function of the different parts of the lungs. Such an analysis is also necessary to form an exact idea about the factors in supraphrenic and infraphrenic diseases which may modify the curve in any part of the diaphragm.

DISCUSSION

Dr. Meltzer said that while he could not in detail follow the very keen analysis of the lung mechanism wherewith Dr. Hoover had brought out such interesting diagnostic landmarks, the speaker and his associates had about a year since made some studies in fowls, with respect partly to their nervous organization, and had observed in them entire absence of diaphragm. He thought that many conclusions are well supported by observing the movements of the ribs in the fowl.

Dr. Jacobi said he would like to give Dr. Hoover a little more work to do. He had not at all alluded to the upper portion of the thorax, having confined his paper exclusively to the lower portion. He would direct his attention to the work that had been done by Wilhelmi Alexander Freund, who, while now eighty-four years old, is still working on subjects wherein he was interested in 1859. This savant has returned to those studies and is as young as ever he was, so it is worth while to now and then refer to him.

What he says has been proved and is confirmed by the speaker's own observation: The premature ossification of the upper aperture of the young thorax, resulting in the shortening and narrowing of the space afforded in the upper part, is a condition finally giving rise to tuberculosis and emphysema. A number of operations have been devised to overcome this emphysema of later years, and with fair results. A number of such operations have been performed in New York also. What the authority cited says, is that the contents of the thorax may in this way be enlarged by an operation and emphysema thus cured. Said authority is now, at eighty-four years, retired, as he ought to be, but is constantly working in the laboratories of Hansemann and issuing publications himself and through his pupils, Hart and others, on the same subject. The speaker asked Dr. Hoover to go over this literature and present his enriched experience at the thirty-third meeting.

Dr. Hoover (closing) called attention to one instance in which the comparative movements of the sides manifested a very interesting balance between the diaphragm and the intercostals that controlled the costal margin. The patient in said instance (a man), suffering from a subphrenic abscess, had an enlargement of the liver in an upward direction. The liver did not come below the costal margin; but this man had a persistent hiccough. The interesting thing was to see the right costal margin move out with every hiccough and the left move in. The arch of his right diaphragm was accentuated just far enough so that when he hiccoughed and the diaphragm and the intercostals were simultaneously activated, the diaphragm had control of the left margin, but it lost control of the right margin.

A POSSIBLE EXPLANATION FOR THE CYANOSIS AND HYPERPNEA SEEN IN PNEUMONIA AND CARDIAC DECOMPENSATION

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In normal individuals the minute volume of the respired air is, primarily, determined by the amount of carbon dioxide, and, secondarily, by the amount of oxygen present in the blood coursing through the respiratory center. Lack of oxygen is a much less effective stimulus to the center than is a corresponding increase in the carbon dioxide of the blood. An impairment in the gas exchange in the lung, so that the blood leaves the heart with too little oxygen and too much carbon dioxide, will cause the blood to be dark or cyanotic and the respiratory center to increase the minute volume of the respired air. This results in a lowering of the percentage of the carbon dioxide in the alveolar air or its concentration in the arterial blood. Whether the oxygen content is affected will depend upon the nature of the respiratory lesion, as will be pointed out later. This type of cyanosis is primarily arterial and the hyperpnea is caused by too much carbon dioxide in the arterial blood. We believe that this type is present in cases of pneumonia who are cyanotic without evidence of air hunger or cardiac impairment, and that it is essentially like that found in congenital heart disease.

In cardiac decompensation without respiratory impairment the minute volume of the blood circulating through the lungs and the respiratory center is diminished, and, if metabolism is normal, the blood per unit volume must carry more oxygen to the tissues and

more carbon dioxide from the tissues than under normal conditions. If the oxygen supply is greatly diminished the excitability of the respiratory center is increased, and in case the blood supply is not sufficient to promptly carry away the carbon dioxide produced the center is abnormally stimulated. The compensating mechanism, brought about by increasing the minute volume of air respired, is the lowering of the carbon dioxide in the arterial blood entering the center to such a degree that the blood as it passes through the center is able, in spite of its small volume, to carry away the carbon dioxide formed without increasing the carbon-dioxide tension in the center. The oxygen content of the venous blood, however, is much less than under normal conditions, inasmuch as the hemoglobin has been compelled to give up a greater percentage of its oxygen. The venous blood is therefore dark or cyanotic. Peabody[1] has shown that the respiratory center of patients suffering with cardiac decompensation is much more sensitive than normally to changes in the carbon-dioxide tension of the alveolar air.

Ordinarily the alveolar air has the same pressure of carbon dioxide as does arterial blood, and the determination of this factor in either will give its value in the other. The direct relationship between the combined and the free carbonates of the blood and the tension of carbon dioxide in the alveolar air in normal individuals is well established. For this reason the method devised by Van Slyke[2] for the determination of the total blood carbonates is capable of giving fairly accurately the tension of carbon dioxide in the alveolar air as determined by various methods.

Walker and Frothingham[3] have published a rather extensive series of cases in which they compared the carbon dioxide in the alveolar air, as determined by the Plesch method, with the carbon dioxide in the venous blood, as determined by the method of Van Slyke. They conclude that the two methods give approximately the same results, and found the most marked variations in their cases of pneumonia and Graves's disease. In these diseases, because of the increased rate of metabolism, Plesch's method undoubtedly gives too high results.

The methods for determining the percentage of carbon dioxide in the alveolar air are not very satisfactory for accurate clinical

use. Haldane and Priestley's method,[4] while it has yielded most valuable data in the physiology of the regulation of the respiration, is not a satisfactory clinical method and does not give very accurate figures in all conditions. By making use of the mathematical laws of vanishing small quantities I have devised a method for the determination of the dead space and the percentage gaseous composition of the alveolar air.[5] I have used this principle for a year and have only recently discovered that Professor Almeida, of the University of Rio Janeiro, has published a preliminary announcement of a method for the determination of the carbon dioxide in the alveolar air which is based on the principle I have used. Priority of discovery therefore belongs to him. Briefly, the principle of the method depends on the influence which the atmospheric air of the dead space has in diluting the gases of the alveolar air in the total expired air. The principle can be shown graphically by the use of a curve, the abscissæ of which represent the amount of the expiration in cubic centimeters and the ordinates the percentage of carbon dioxide or oxygen in the expired sample. The larger the expiration the greater percentage of carbon dioxide does the air contain and the less percentage of oxygen, because the diluting factor which the dead space adds becomes less and less important as the expiration increases in amount. By making several observations in which the expirations are progressively increased it will be seen that the percentage of either the carbon dioxide or the oxygen, when plotted on cross-section paper, gives a perfect hyperbolic curve in which two constants are present: one is the percentage of carbon dioxide in the alveolar air and is represented by the horizontal asymptote, and the other the capacity of the dead space, which is represented by the vertical asymptote.

The percentage of carbon dioxide in the alveolar air as determined by this method is a trifle lower than that obtained by other methods in use at the present time. However, it is more accurate because it has not the theoretical errors present in other methods, and, although involving a greater time and more complicated apparatus to carry out, it requires less coöperation on the part of the patient than do the other methods.

In the Lakeside medical service we have been using this method

to determine the percentage of carbon dioxide in the alveolar air in company with Van Slyke's method for the determination of the blood carbonates in a number of cases of pneumonia and cardio-renal disease. Our series is not large enough to warrant a complete report, but the results so far obtained throw some new light on the pathological physiology of these diseases.

In several cases of pneumonia in which cyanosis was present without signs of cardiac impairment or air hunger we have noted that the carbon-dioxide tension of the alveolar air as determined by our method is decidedly lower than that obtained by Van Slyke's method. In the greater number of pneumonias seen late in the disease and without cardiac impairment we found that the blood carbonates and the alveolar air carbon-dioxide determinations by the two methods corresponded fairly well. Cyanosis in these cases was never marked.

Especially interesting is one case whom I saw twenty-four hours after the onset of the attack. His right base was dull, with high-pitched bronchial breathing. His respirations were 28 to the minute, pulse 115, and temperature 104°. The man appeared very ill, but was able to coöperate with me and was fairly comfortable. He had no signs of cardiac impairment and the blood-pressure was 135 systolic and 85 diastolic. The most noticeable thing about him was the intense *cyanosis*, which was present without symptoms of respiratory distress.

Examination of his blood by the Van Slyke method showed practically a normal blood carbonate reserve, and the alveolar air as estimated by this method gave 37.5 mm. Hg. carbon-dioxide pressure. His alveolar carbon dioxide determined by my method was 26 mm. The following day his general condition was much worse. The right upper was consolidated, his temperature 105°, pulse 140, and his blood-pressure a little lower. His cyanosis had disappeared. He was irrational and I could not obtain a sample of air for carbon-dioxide determination of the alveolar air. His blood carbonates were, however, the same as the day before. We believe that an explanation of the cyanosis and the disappearance of it as the patient grew worse may be found in a consideration of the respiratory physiology of congenital heart disease.

Last year Dr. Julius Hess and I[6] reported 3 cases of congenital heart disease occurring in boys of the same family. In all we found a low percentage of carbon dioxide in the alveolar air, an observation which has been found by others in congenital heart disease. The blood carbonates by Van Slyke's method and the venous carbon-dioxide tension by the method of Christiansen, Douglas and Haldane[8] were normal. We are therefore forced to conclude that the blood which enters the lungs of these boys is more completely freed of carbon dioxide than in the normal individual, and that less than the normal amount of blood is passing through the lungs. The blood leaving the lungs therefore carries a full load of oxygen and less than the normal amount of carbon dioxide. On reaching the left heart it mixes with blood coming directly from the right heart through the abnormal connection. This blood is venous blood having a high carbon-dioxide and a low oxygen content. The result of the mixture gives a blood probably almost normal with reference to the carbon-dioxide content, but less than normal with reference to its oxygen content. The boys all have an increased minute volume of respired air, but do not show any evidence of air hunger, nor is their capacity for work much less than that of the normal controls.

We interpreted these findings as indicating that these boys have potentially a condition of carbon-dioxide acidosis, which they compensate for by overventilating the blood which passes through the lungs so that the blood which leaves the left heart may have a normal carbon-dioxide tension. In the case of oxygen, however, since the blood leaving the lungs carries all the oxygen it can carry, no compensation can take place, and the mixture of blood in the arterial system is unsaturated with oxygen, and hence blue in color.

A very similar explanation can be given for the cyanosis which we have observed in pneumonia. Let us assume that the pathological process which destroys the respiratory membrane and makes the exchange of gases impossible in the pneumonic lung precedes the closing of the pulmonary vessels. Such a condition will give physiologically the same conditions as are present in the congenital heart disease. The blood reaching the left ventricle would in this case be a mixture of venous blood from the diseased area and

arterial blood from the sound area of the lungs. The respiratory center, responding to the increase of the carbon-dioxide content of the blood, increases the minute volume of air respired and lowers the carbon-dioxide tension in the arterial blood. This would tend to make the carbon-dioxide concentration of the blood normal, but the oxygen content would be determined by the relative amounts of venous and arterial blood being delivered to the left ventricle. It would always be less than normal, since there is no possible mechanism to increase materially the amount of oxygen which the blood will take up. Such a condition can exist without evidence of air hunger or respiratory distress as long as the oxygen supply is sufficient. However, cyanosis would be present, since the capillary blood is not saturated with oxygen. As the disease progresses the circulation through the involved lungs becomes less and less and the cyanosis disappears.

We find confirming evidence of this view in the studies which Porter and Newburgh[7] have made on the condition of the respiratory center in pneumonia. These investigators find the respiratory center is depressed through a peripheral afferent vagus mechanism. The pneumonic respiratory center, being less sensitive to an increase in the carbon-dioxide content of the blood than is the normal one, requires a larger amount of carbon dioxide in the arterial blood for the effective stimulation of the center. We have found confirmatory proof of this view in the case of one cyanotic patient in whom we found the alveolar carbon dioxide and the blood carbonates to be practically normal, but whose venous blood, as determined by the method of Christiansen, Douglas and Haldane,[8] was higher than normal. This condition indicates that the amount of blood passing over the respiratory membrane was reduced and that the blood entering and leaving the respiratory center had a higher content of carbon dioxide than under ordinary conditions. This offers an explanation for the fact that many cases of pneumonia which are cyanotic because they are receiving unrespired blood in their left heart fail to show much if any decrease in the percentage of carbon dioxide in the alveolar air. That it is found in some cases, however, is significant of its potential existence in all. In other words, were it not for the hypesthesia of the respiratory center which Porter

and Newburgh find present in pneumonia we should probably more often find the alveolar carbon dioxide lower than the blood carbonates indicate. Butterfield and Peabody[9] have furnished some experimental evidence that cyanosis of pneumonia may be caused by the formation of methemoglobin. I do not wish to deny that this occurs, but I believe that the degree of cyanosis which we see developing early in the disease is out of all proportion to the infection. Moreover, the blood of these cyanotic patients, when shaken in the air, assumes a very arterial color, which is in striking contrast to the deep, dark color which persists in the blood of patients who have been poisoned with coal-tar products. One cannot explain the sudden disappearance of the cyanosis in the cases mentioned on the theory of methemoglobin formation. It appears probable to us that the cyanosis disappeared when the amount of unrespired blood which was reaching the left auricle became negligible.

We believe that in these cases of pneumonia which we have described one portion of the blood circulating through the pulmonary vessels consists of blood which has been superventilated, while another portion which passes through the diseased area is unventilated. Therefore the confluence of the total blood in the left auricle gives a mixture of superventilated blood with unrespired blood. This will give a total result of an aortic blood which will have a fairly normal amount of carbon dioxide but a low amount of oxygen. The lack of oxygen is responsible for the cyanosis.

In several cases of cardiac disease we have found the percentage of carbon dioxide in the alveolar air low during the stage of cardiac decompensation. In these cases there was no lowering of the total blood carbonates, and as the heart compensated by rest in bed and treatment the alveolar air carbon dioxide and the blood carbonates came back into agreement. Recently, with Dr. Christie, I have had one case of special interest. The patient was admitted to the ward with a badly decompensated heart, air hunger, orthopnea, high systolic and diastolic blood-pressure, and a dilated heart. His blood carbonates gave a normal figure, indicating no reduction in his blood alkalinity. His minute volume of respired air was 10 liters, and his alveolar air determined directly gave a carbon-dioxide

pressure of 30.7 mm. Hg. His blood failed to show evidence of acidosis, while his alveolar air indicated that it was present. His venous carbon-dioxide pressure, as determined by the method of Christiansen, Douglas and Haldane, was about 46 mm. Hg., a practically normal figure. The wide difference between the pressure of carbon dioxide in his arterial and his venous blood indicates that the blood which was passing through his lungs was being superventilated. In this patient the blood entered the lungs bearing approximately the normal load of carbon dioxide, but left the lung with a less than normal amount of carbon dioxide. It entered with a carbon-dioxide pressure of 46 mm. and left with a carbon-dioxide pressure of 30. Since his blood was approximately normal in its capacity to carry carbon dioxide, we may compute from the above data, together with a determination of his total respiratory exchange, the minute blood flow through his lungs from the data furnished by Christiansen, Douglas and Haldane[8] on the relationship between the oxygen and carbon-dioxide content of the blood. I have done this and find that each 100 c.c. of blood which passed through this man's lung lost at least 10 c.c. of carbon dioxide. The normal figure given by most authorities is about 6 c.c. This figure, taken together with the total carbon dioxide eliminated by the patient per minute, which in this case was a normal figure, gives him a minute cardiac output of about 3 liters per minute, which is about one-half the calculated normal figure. Because of the small amount of blood which passes through the respiratory center the metabolism of the respiratory center itself would cause the tension of carbon dioxide to be raised above a normal level unless the blood entering it is capable of carrying away more carbon dioxide than it does under normal conditions.

Lewis[10] observed similar cases, and Peabody[1] has reported a series of cases which undoubtedly fall into this group. Lewis believes that the cyanosis and dyspnea without acidosis are due to poor oxygenation of the tissues. Peabody, basing his conclusions on the low alveolar carbon-dioxide pressure present in these cases, believes that there may be an actual acidosis. He, however, recognizes the role which the accumulation of carbon dioxide in the respiratory center may play in the production of the dyspnea. Recently,

Peters[11] reported similar cases, but attributes them to a failure in the gas exchange in the lungs. He did not take into consideration the fact that, if the respiratory exchange and the carbon-dioxide tension of the blood leaving the lungs remain constant, a reduction in the minute volume of the blood must result in an increase in the tension of carbon dioxide in the venous blood. His explanation fails to apply in our case for the following reasons: the respiratory exchange and the tension of the carbon dioxide in the venous blood were nearly the same during and following the stage of decompensation, and there can hardly be any doubt as to the fact that the mass movement of the blood was greatly impaired in our case. From both a physical and a physiological stand-point we believe our explanation is more plausible than his, and he is quite right in believing that these cases are examples of a carbon-dioxide acidosis.

From the above results we see that the percentage of carbon dioxide in the alveolar air is not a good guide as to blood acidosis, at least in cardiac disease, pneumonia, and congenital heart disease. In the cardiac case a low carbon-dioxide tension in the alveolar air is the result of an attempt of the respiratory center to prevent its venous carbon-dioxide pressure from being raised on account of the slow circulation. In pneumonia and congenital heart disease the respiratory center reacts to keep the arterial blood at a normal carbon-dioxide tension.

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DISCUSSION

Dr. Hoover had one statement to make about the piling of unrespired blood into the left ventricle in cases of pneumonia, assuming that the pulmonary circulation throughout the consolidated lung remained open. Of course the point is problematical, but an interesting determination in all our cases of pneumonia would be, how much blood is going through the pulmonary circulation (the consolidated area) and how much are the pulmonary vessels engorged? One of the experiences of the authors has been the observing of very large emboli in cases of pneumonia who have not been very ill. We have seen one case of a very large embolus which had so contracted the axillary and brachial arteries that the patient had to have his arm amputated. The only conceivable source of the embolus was from the pulmonary vein. The authors think that possibly the cyanosis in some cases of pneumonia may be dependent directly upon how much unrespired blood is being poured into the left ventricle.

A very simple confirmatory procedure adopted by the authors, and one which gave a most satisfactory result, was to take a dog and to tampon his right bronchus with a lamb's wool tampon. This was done by pushing the tampon far down into his right bronchus, thus shutting off all the ventilation in his right lung, but in no way affecting the blood going through the right lung. The blood therefore in the left ventricle was a mixture of venous and arterial blood. That this was the case was shown by receiving samples of the animal's blood from an artery directly into a test-tube under oil, so that the gases of the blood would be unmodified, and then stopping the bronchus and again collecting his blood. In a proper light one could see that the blood was dark when the bronchus was closed, but when the plug was removed the blood was light again. By this process the authors could produce cyanosis at will.

Dr. Meltzer directed attention to the difference in the color between cyanosis due to oxygen want and cyanosis due to increased CO_2. When there is a want of oxygen the patient has a leaden ashy-gray color, and is not really blue. Cyanosis with a deep blue color is due to the presence of an abnormal amount of carbon dioxide in the blood. The speaker says that nevertheless the efficient administration of oxygen affects favorably both forms of cyanosis. By using his apparatus for oral rhythmic insufflation of oxygen he has seen patients in a dying condition who looked deep blue or ashy gray change their color within a short time and in many instances became actually pink in appearance.

SOME POINTS RESPECTING THE LOCALIZATION OF SYPHILIS ON THE AORTA

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Ever since Vesalius first described internal aneurysm, referring particularly to aneurysms of the thorax, numerous observations have been made upon the manner of origin and the seat of aneurysm upon the aorta. For many years statistics have been collected indicating the frequency with which aneurysms are found upon different arteries, in a hope that the anatomical distribution of these lesions would give some clue for their occurrence. Although Pare observed that internal aneurysm was not uncommonly associated with the pox, irrefutable evidence of the importance of this disease for the development of aneurysm was not established until 1875 when Francis Welch, in his study of syphilis occurring in the army, described a specific type of reaction in the aorta resulting from lues. For a time following the observations of Welch little support was given to his statement but during the last few decades the truth of his findings has been confirmed by many authors by different methods of analysis. The earlier studies dealt with the naked-eye appearance of the aorta which, when it was involved in syphilitic disease, showed characters quite distinctive and different from those seen in arteriosclerosis. Then, too, the microscope assisted in defining a type of lesion peculiar to syphilis and distinguishable from other diseases of the arteries. True gummata were also occasionally found, leaving no doubt as to the nature of the process acting upon the arterial wall and eventually bringing about such weakening as to permit of aneurysm. The final demon-

stration of the spirochete in a variety of arterial affections removed all question concerning the localization of the virus of syphilis in the tissues of the aorta and other vessels.

At first sight it would appear that the problem of syphilis and the arteries has been completely unfolded in the progressive steps illustrated in the many studies since the days of Pare. Most of the work has been developed in logical sequence from the early and rather gross observations to the minutiæ of histology and bacteriology. We recognize fully the clinical importance of syphilis as a systemic disease and have many means for the diagnosis of its presence and for the discovery of its relatively early localization upon the arteries. We are, furthermore, aware that the localization of syphilis upon the vessels occurs with greater frequency in certain arteries, the aorta and cerebral vessels, than in others, as well as that the infection occurs in certain regions of these arteries with greater frequency than elsewhere. The predilection of the syphilitic virus for localizing in distinct districts in the aorta has always received much comment. It is true not only that aneurysm of syphilitic origin locates most commonly on the first part of the aorta but also that syphilitic aortitis in the earliest stages of its development is seen with equal frequency on this portion of the vessel. The mechanical theory of aneurysm which placed greater stress for the production of aneurysm upon the effect of high blood-pressure or, as others would have it, upon the effect of the velocity of currents, than upon the disease in the wall of the artery, had for a time enticed our attention into channels of thought and theory no longer tenable with the newer studies. Granted, of course, that two factors must be available for the development of aneurysm, first the weakening of the vessel wall and second the presence of a blood-pressure (normal, subnormal or excessive), we must not lose sight of the fact that for the development of true aneurysm, the presence of a localized weakening of the artery is of first importance. It is only a weakened vessel which can develop aneurysm; hence, appreciating that the spirochete of syphilis is the most common damaging agent of the aortic wall, the important point occupying our attention is, why should it localize with such great frequency in isolated segments of the aorta? There is nothing in the character of the tissue of the

aorta which could lead us to believe that the chemical characters of particular portions offer a better nidus for the infection, nor is there anything in respect to the microörganism whereby preference would be shown in localizing in one or other portion of the vessel.

The common localization of syphilitic arteritis upon the ascending aorta with the transverse and descending thoracic aorta following next in frequency is now well known. The aortitis beginning in the first portion of the aorta usually localizes at a point just above the aortic ring and then spreads with considerable rapidity along the arch of the aorta for variable distances. The lesion also makes its way in the opposite direction, so that the tissues at the aortic orifice, particularly the valve leaflets, become more or less involved. The spread toward the heart, however, progresses more slowly and we have several examples where, although there was clinical evidence of incompetency of the aortic valve, this was due not to disease upon the aortic valves but to a stretching of the aortic ring. In these instances the syphilitic disease of the aorta stopped fairly abruptly at the upper margin of the sinuses of Valsalva and did not produce any lesion in the aortic tissues contained within the heart. An interesting feature of the syphilitic process of the aorta is the sharp line of demarcation which separates the diseased area from the healthy. This boundary marks the advancing border of the syphilitic process extending to occupy new tissue. The involved aortic wall with its marked thickening, corrugation and scarring is also in sharp contrast to the aorta in other portions. This contrast is decided whether the non-syphilitic areas show scleroses of other kinds or not. The syphilitic process does not come to occupy any particular face in the circumference of the aorta and thus does not show a characteristic distribution like the nodular endarteritis which is so commonly observed in the vicinity of the mouths of the intercostals and at the entrance of the ductus arteriosus. The syphilitic process almost always surrounds the lumen, though, as we have pointed out before, the intensity of the involvement at particular points differs in the individual cases.

Another peculiar feature of syphilis of the aorta is the infrequency with which two foci develop concurrently upon separate portions of the aorta. Occasionally, a dual localization is found to

have occurred, one in the thoracic portion and the other in the abdominal. Less frequently two separate foci occur within the thorax itself; and for the moment I do not recollect ever having seen such a condition recorded. At first sight it might suggest itself that, because aneurysm is sometimes encountered with multiple sacs, one, it may be, situated upon the ascending aorta, a second upon the transverse, and a third upon the descending thoracic, we are dealing in such an instance with separate localizations of the syphilitic virus. Careful examination of these specimens demonstrates that the syphilitic process is diffusely disseminated over the entire thoracic aorta and that the aneurysms have individually developed at situations where local damage has advanced more than in the remaining portions of the arterial wall. That individual and isolated infection may occur in different portions of the aorta is not to be denied, but where this takes place within the thorax, the lesions in their early stages progress with such rapidity that they fuse at their borders and can no longer be distinguished as separate occurrences. The occasional double localization upon the aorta is seen where a specific infection has involved the first portion of the thoracic aorta while a second attack has occurred in the abdominal aorta, usually in the vicinity of the celiac axis. Under such circumstances a portion of aorta free from luetic change intervenes between the two foci. It is possible that a relationship between the two lesions may exist but up to the present it has not been demonstrated. Broadly speaking, however, the syphilitic attack upon the arterial wall differs very materially in its distribution from that of ordinary arteriosclerosis and endarteritis. The syphilitic lesion may occur simply as a patch of greater or less extent, the progress of which is dependent upon the lateral spread from that patch as well as upon the intensity with which the arterial wall is affected by the disease. On the other hand, the more common arteriosclerotic affections are not so constant as to the particular portion of the aorta in which they locate and for them it is the rule to appear at multiple sites with lesions which are quite distinct and unrelated.

Our attention has been attracted, both from postmortem studies and experiment, to the part played by the lymphatics in disseminat-

ing syphilitic and other infections along the course of various arteries. We have found that the lymphatic channels of the outer wall of the aorta form a fairly intricate system which communicates with neighboring lymph glands. This system of channels may be demonstrated by injection experiments whereby the interlacing communications stand out quite prominently. From these injection experiments it would appear that the most profuse system of channels is found in those positions of the aortic wall which lie in closest relation to the neighboring lymph glands, while as a greater distance is interposed between the lymph gland and the area provided a smaller number of lymphatic vessels is to be demonstrated. This is particularly evident in the descending thoracic aorta where a portion of the aortic wall is free and unattached, whereas its posterior and lateral portion lying close to the vertebral column is in close proximity to the lymph glands of this region.

If we follow the aorta from its beginning we find that its first portion lying within the pericardial sac appears to have lymphatic channels in common with the pericardium as it is reflected over it. Macroscopic lymph glands have not been demonstrated between the pericardium and the aortic wall. Directly over the pericardial sac where it is reflected from the aorta to become the parietal pericardium, and lying along the left lateral border of the ascending aorta, are a group of lymph glands which communicate with other glands in the anterior mediastinum and which, furthermore, supply this portion of the aorta. In this region the anterior and left border of the aorta appears to have a richer supply of lymphatic vessels than the right border. About the arch of the aorta there are a number of lymphatic groups, each of which has abundant communication with the aortic wall. The ascending arch has lymphatic connections particularly with glands in the anterior mediastinum, while the transverse arch has a drainage both to the mediastinal glands and to those about the right border of the trachea. The descending arch receives lymphatics from the glands along the left border of the trachea as well as from the glands at its bifurcation. As we pass to the descending thoracic aorta we find a variable number of lymph nodes lying along the border of the aorta and particularly on the right side. The lymph channels from these

nodes form a plexus about the exit of the intercostal arteries and advance in single lines around the anterior and free portion of the aortic wall. In the abdominal aorta an intricate plexus of lymph channels is found in the region of the celiac axis which supplies fairly uniformly the aorta in its entire circumference. In the lower portion the aorta receives a rich supply of lymphatics from the retroperitoneal lymph glands which lie along each border of the aorta. These lymphatic channels of the aortic wall lie for the most part in the adventitia, in close relation to and following the course of the fine nutrient vessels which are found in this structure. As the denser portion of the aortic wall is approached the lymphatic vessels become fewer in number and extend only as very fine structures into the adventitia as it adjoins the media. The one feature that is striking is that the lymphatic supply of the aortic wall is not uniformly disposed. In certain portions a much richer supply of lymph vessels can be demonstrated. These ramify in an arborescent or stellate manner, leaving other portions of the aortic wall with a more meager distribution.

To determine the part played by the lymphatics in conveying infection about the arterial walls, bacteria were inoculated into the loose tissue of the mediastinum of rabbits. The organisms used were varieties of streptococci, chiefly of the viridans group. In these experiments it was found that the microörganisms after setting up a localized reaction at the point of inoculation migrated in various directions, most rapidly along the flow of the lymph to the neighboring glands. Gradually, however, the dissemination was of a retrograde character, whereby the microörganisms followed the lymphatics into the various tissues in the vicinity. Thus, the infection was found to follow the fine channels passing about the aorta as well as the structures at the hilus of the lungs. In the rabbit, however, the lymphatics are not nearly so numerous about the aorta as they are in man. The small-sized aorta in these animals is poorly supplied by vasa vasorum which penetrate to the media, but the adventitial vessels are well marked. Yet the results of the experiments were sufficiently clear to indicate a distribution of the infection by way of the lymphatics to the large vascular trunks of the thorax.

A similar but clearer evidence of the lymphatic distribution of infection was obtained in man. It was found that in the severe cases of pneumonia coming to autopsy, an almost constant infection of the glands of the anterior mediastinum was to be noted. Under these conditions the lymphatics stand out prominently, the glands are swollen and succulent, and great chains of them can be traced along the trachea and its bifurcation, as well as below the arch of the aorta. The tissues are usually loose and edematous, and if the autopsy has been held shortly after death, the subject is a favorable one for demonstrating by the injection method the course of the lymphatics. But more than this, the infecting agent, the pneumococcus, may be isolated from the tissues along the course of the lymphatics and even up to and in the tissues of the outer portion of the aortic wall. Such infections in the aortic wall have previously been demonstrated by Andrewes, and are in accord with our own previous studies in which inflammatory reactions have been observed to follow the course of the nutrient vessels in typhoid fever, acute rheumatic fever, pneumonia and sepsis. In other words, those inflammatory reactions which we have described as types of acute non-suppurative mesarteritis are the result of infection by various bacteria localizing upon the aortic wall by way of the lymphatics.

Further examples illustrating the progress of a bacterial virus along the periarterial lymphatics, are readily at hand. The importance of these perivascular channels is also illustrated in the spread of the infection in periarteritis nodosa where it may be shown that the involvement of an artery results from the passage of the infection along the lymphatics to the ramifications of that particular artery. We were able to observe this in two cases in which the hepatic artery with its branches was the seat of an acute progressive inflammatory lesion. In a like manner, one can readily follow the perivascular migration of infection in the arteries of the meninges. Here it will be found that the infecting agent and the inflammatory exudate progress along the course of the meningeal arteries as they lie embedded in tissue and that this reaction in the lymph spaces precedes the appearance of the exudate in the larger spaces or caverns of the meningeal folds. Likewise and of better illustration is the similar reaction which follows the course of the nutrient vessels

passing from the meninges into the brain substance. Similarly the importance of the lymphatic channels, particularly of those surrounding the nutrient vessels of tissues, may be cited in reference to the myocardium and kidney. These are of course common observations, but for the most part we have not been recognizing their importance from the view-point of the further dissemination of the virus nor from the stand-point that when the infectious agent is in such close proximity to arteries of various sizes, actual infection of the arterial wall is liable to occur.

If we again revert to our problem respecting the localization of infection in the aortic wall, we must emphasize these three anatomical conditions: (1) as we have pointed out that there are certain regions along the course of the aorta in which the arrangement of the lymphatic channels is more complex and their number far greater than in other portions; (2) that the aortic wall itself is richly supplied with nutrient vessels, the vasa vasorum, each of which has a liberal lymphatic drainage following its course; and (3) that these lymphatics are in direct association with the larger lymphatic system which surrounds the aorta as a whole and which has two large drainage beds, one in the thorax and one in the abdomen. It is in relation to these drainage beds that the syphilitic virus comes to be distributed to particular segments of the aorta.

The route followed by an infection and the advance of the reaction from one tissue to another can be followed much more readily when the invasion is due to bacteria causing acute responses, than when the reactions are more chronic and come under observation only in the later stages of the lesions. This is particularly true in the case of syphilis, in which we rarely recognize the earliest metastatic lesions. Syphilis of the aorta has rarely been observed at a time before the typical changes of the inner or intimal surface are quite distinct. Under these conditions we must appreciate that the syphilitic process of the vessel wall is quite late and advanced, while many of the reactions involving different structures in the infection have been obliterated by the secondary fibrosis. Nevertheless, with some care the track of the reactions may still be followed both within the vessel wall and in the surrounding tissue. In a few cases we attempted to follow the relation of the inflamma-

tory process as it made its way along the vasa vasorum from the periarterial structures to the vessel wall proper. Under these conditions it was not difficult to demonstrate a chronic mediastinitis which, though of very irregular distribution, nevertheless had a distinct course along lymphatic channels to and from the mediastinal lymph glands. These inflammatory processes appeared mild in degree and would not have attracted attention save that in following the channels more closely it was found that periodic exacerbations occurred along their tracks. A varying amount of fibrosis was the outcome of the reaction. Where the more aggravated response led to local cellular infiltration occasional true gummata appeared. It was, however, quite unusual to find marked gummatous destruction of the mediastinal tissues; in fact we have observed this in only one instance. The lymph glands themselves may respond in the earlier stages of the disease by hyperplasia but we have found it unusual for these glands to enlarge to such a degree that they would clinically or even pathologically attract attention. During the subsequent process of the syphilitic infection the diffuse fibrosis that is observed in the mediastinum also occupies in some degree the lymph nodes.

By thus localizing in the mediastinum, the syphilitic virus has an opportunity of attacking to greater or less degree the important visceral contents of this division of the thorax. The most accessible and important structure is the aorta. The heart itself is peculiarly isolated so that, although it has an extensive lymphatic drainage, it has no dominant compensatory lymphatics advancing upon it from the parietal pericardium. The only region in which accessory lymphatics become available is at the base where the parietal pericardium is reflected directly upon the great vessels. The trachea and large bronchi, which lie in close relation to the lymphatic system of the mediastinum, show a considerable immunity to the localization of the syphilitic virus. The ascending limb and arch of the aorta, on the other hand, are themselves surrounded by a network of lymphatic and bloodvessels and present a vulnerable tissue for the spirochete. Thus with the localization of the syphilitic virus in the rich lymphatic bed of the thorax, it becomes almost certain that the infection will also involve the tissues of the aorta.

The close relation between the luetic inflammatory processes of the mediastinum and those of the aortic wall is also shown in the late fibroses which lead to such unusual thickening of the arterial coat and which, furthermore, bind the aorta firmly in its mediastinal bed. The thickening of the aortic wall, when involved in syphilis, is the result of a connective-tissue overgrowth in part situated in the intima and media but for the most part lying in the adventitia and binding this structure to the neighboring periarterial tissues. Syphilitic aortitis has always an associated syphilitic periarteritis. As previously stated, we do not often have the opportunity of tracing the early inflammatory responses which communicate between the mediastinum and the aortic wall, but there is always the evidence in the late cases of reparative fibrosis which distorts the vascular structures. Of course in the presence of aneurysm, one must be guarded in distinguishing the fibrosis which has resulted from the syphilitic virus from that which has resulted secondarily to the presence of aneurysm from mechanical irritation.

Though we feel confident of the important part played by the lymphatic system of the thorax in localizing syphilis to distinct portions of the arterial wall, it is not clear as yet why and in what manner the virus finds its way to this particular region of the body. By analogy and in comparison with certain other infections, it is probable that the systemic distribution of the spirochete is accomplished by the blood stream. As with other infections, certain tissues and structures are more receptive for the metastatic infection than others. In some instances the localization of the infection may be associated with trauma, but this can hardly be a factor within the chest. Up to the present time animal experimentation has given no clue suggesting the reason for the thoracic metastasis in man. It is probable that the selection of the mediastinum by this infection is bound up with the question of the biological properties of the microörganism and the favorable conditions presented by particular tissues for its growth.

THE CLINICAL USE OF FOREIGN PROTEIN

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In considering the possible non-specific elements in the phenomena of disease, it is not proposed to supplant the older ideas of specificity, but to discover in what ways these non-specific reactions help or hinder the specific factors, or act independently of them.

Studies of the changes brought about in the animal body by the introduction of foreign protein have not only developed new conceptions, such as those of the mobilization of serum protease and the relation of normal ferment and antiferment, which seem destined to throw light upon a number of unexplained phenomena of disease, but have also broadened our views in regard to the older theories of the more specific factors.

In this discussion of the effects of foreign protein in disease our interest centers in two main topics: (1) The relation of the phenomena observed to those which occur in the natural recovery from disease. (2) The clinical results which follow the use of foreign protein in disease. At some time in the future it may be possible to discuss these two together, but for the present it seems essential to safety to deal with them separately.

1. Specificity in biological reactions has been the guiding principle of those who have attempted to devise methods of study and therapy of infectious diseases, and while modifications in the original theory of antigen and antibody have from time to time been found necessary, it is along this line that most of the progress to within the past years has been made.

The recognition of the importance of less closely specific and more general phenomena in disease is comparatively recent, though

it may be said to have begun years ago with the studies of Vaughan on protein-split products. The non-specific changes which occur in the body in response to the injection of foreign protein and the methods of their demonstration have been well described by Jobling.

While the reactions which we speak of as specific differ from those we call non-specific, in the conditions and methods of demonstration we may conceive of both classes as dependent on physico-chemical principles, differing only in the degree of fineness of their adjustment.

The recently reported observations of Hektoen[1] approach this problem of the changes produced in response to alien protein from still another angle, and form a sort of bridge between the specific and non-specific.

Hektoen found that "the introduction of horse blood or serum in rabbits treated a considerable time previously (five months) with sheep blood resulted in the production not only of precipitin for horse protein but also for sheep protein, as well as for proteins of several other species."

This renewed appearance of sheep precipitin following the injection of horse serum occurred several weeks after sheep precipitin present in response to previous injection of sheep serum had disappeared from the blood.

In another rabbit previously injected with human blood, the injection of horse serum caused the reappearance of precipitin for human serum.

Other experiments with other proteins in other species of animals gave similar results.

These findings indicate that in carefully controlled animals the introduction of one antigenic substance may cause the appearance not only of antibodies specific to the recently injected antigen but also antibodies specific to another different antigen in an animal previously sensitized to this latter antigen. We must remember, however, that in a serum we introduce many antigenic substances, and a second serum injected may contain among its constituents

[1] Precipitin Production in Allergic Rabbits.

some substance, perhaps in minute amount, which was also present in the first serum.

Bacterial antigens in suitably prepared rabbits have been found by Conradi and Bieling[1] to produce like results. Rabbits were injected with typhoid bacilli; later, injections with colon, dysentery, or diphtheria bacilli were followed by renewed formation of typhoid agglutinin. In persons inoculated against typhoid fever or in those who had had typhoid fever, the occurrence of other diseases, such as malaria, pneumonia, erysipelas, or miliary tuberculosis, was followed by increased typhoid agglutinin.

The recognition of this interrelation of specific and non-specific reactions is an important step in understanding the problems of the effects of foreign protein in infections and of the effect of one infection upon another in the human body. It is quite possible that phenomena such as these which at present appear to be what we now call non-specific may turn out to be specific, arising in response to a specific antigenic fraction in the injected material in an animal previously sensitized or made highly reactive by previous infections.

2. I come now to the question, To what extent do results warrant the use of intravenous injections of foreign protein in infections, especially typhoid fever and arthritis?

Published reports of clinical results after the intravenous injection of foreign protein in patients suffering from infectious diseases have led to a widespread employment of the procedure, especially in arthritis, often by those untrained and uncritical in judgment.

In typhoid fever a number of favorable reports have appeared. In a very limited number of cases studied by workers in the Memorial Institute for Infectious Diseases, instances of critical fall in temperature with clinical improvement, as well as failure to modify the course of the disease in other cases have been noted. On the basis of our own observations and those of others we have not felt justified in further extending our use of this procedure in typhoid fever, though from a statistical point of view the number of cases is small.

[1] Deutsch. med. Wchnschr., 1916, xlii, 1280.

In patients suffering from arthritis very striking amelioration of pain and swelling in joints have been noted following the reaction produced by the intravenous injection of bacterial or other foreign protein. I have had occasion to observe a number of cases of infectious arthritis so treated by others. Some of those who improved following the injections later returned as badly crippled as before. When the infectious cause of their arthritis was removed, where this was possible, they again improved, and this time did not return. There is always the danger that the routine use of a non-specific remedy may lead to the incomplete or careless study of patients.

But in addition to weighing the successes and failures in the alleviation of the symptoms of disease, we must also consider the other effects of the injection upon patients. It is perhaps difficult to estimate the probable remote effects of the introduction of foreign protein and the attendant shock upon the kidney and other organs, though there is some evidence that such unfavorable effects are produced. However, the immediate effects are evident and often alarming. Cardiac dilatation, hemorrhages from the nose or intestine due apparently to vascular change rather than to alteration in coagulation time of the blood have been noted, and death has occurred in some cases. It is probable that the number of deaths throughout the country is much greater than reports would indicate.

I wish to refer to three instances in one hospital within six months in which patients died following intravenous injections of bacterial protein. I did not see the patients, but fairly complete clinical records with necropsy records in two of them are available. All 3 patients were young adults in whom there was no evidence of previous cardiac, renal, or vascular disease.

A woman, aged twenty-six years, suffering from gonococcal arthritis of moderate severity, received an intravenous injection of 0.33+ c.c. of a rather heavy suspension of killed meningococci without reaction or symptoms. Three days later she received 0.5 c.c. of a suspension of killed meningococci at 10.25 A.M. Chill and fever and rapid pulse followed. At 7 P.M. a large amount of fluid was aspirated from the dilated stomach. She became irrational,

with muttering delirum and small, weak pulse. The urine, previously normal, was suppressed, only one ounce being secreted in thirty hours. Death thirty-six hours after the injection. At necropsy in addition to the arthritis, dilatation of the stomach, thrombosis of a branch of the left renal artery, and hyperemia of the brain capillaries were found.

A man, aged twenty-nine years, entered the hospital for a recurrent arthritis of three months' duration. He was not acutely ill and had very little fever. Heart and lungs appeared normal. Blood-pressure, 138, diastolic 78. At 4.45 P.M. he received 0.5 c.c. of a heavy suspension of killed typhoid bacilli (1 c.c. = 10,000,000,000) by intravenous injection. At 5.25 he had a severe chill and the temperature rose to 105.4°. Epistaxis at 6.45 and vomiting of brownish material at 8 P.M. He died at 9.20, about five hours after the injection. No necropsy.

A woman, aged thirty-eight years, was admitted to the hospital suffering from typhoid fever. In addition to typical history and fever curve, examination disclosed rose spots and enlarged spleen, and typhoid bacilli were isolated from the blood. About the end of the second week, at 9.50 A.M., she received by intravenous injection 5 minims (0.33+ c.c.) of a suspension of killed meningococci. At 10.05 she had a violent chill and by 11.05 the pulse was imperceptible and the temperature 107°. At 11.50 epistaxis occurred and a large bloody stool was passed. She died at 1.45 P.M., four hours after injection. At necropsy, in addition to typhoidal ulceration of the bowel, with hyperplasia of lymph follicles and a moderate edema and atrophic emphysema of the lungs, there were found punctate hemorrhages throughout the brain substance and a subconjunctival hemorrhage of the left eye. No gross pathological changes in the heart.

In all 3 cases the dose of killed organisms was evidently excessive, and might not have been employed by one more skilled in this type of work, although other patients received equally large doses. Nevertheless this occurred under conditions of control much better than those which obtain in localities more remote from medical centers.

Pathologically the thrombosis of the renal artery in 1 case,

and the multiple hemorrhages in the brain substance and conjunctiva associated with epistaxis and intestinal hemorrhage during life in the other are of interest.

The study of the non-specific elements in disease is of great importance, perhaps greater than we now realize, and promises to open for us new avenues of attack.

From a therapeutic point of view, however, I believe we should warn against the indiscriminate and routine use of these methods until they have been more thoroughly studied and the dangers as well as the reputed advantages better defined.

A ROENTGENOLOGIC STUDY OF THE EFFECTS OF DUST INHALATION UPON THE LUNGS

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The possible pathologic features and the various causes of increased thickness of the prominent linear shadows, especially those extending from the hilus to the base, of so many individuals examined for tuberculosis and other conditions have been questions about which more or less doubt has existed. Furthermore, it is frequently difficult to assign to their exact diagnostic value in the detection of early pulmonary tuberculosis the more isolated thickened trunk shadows often found in the apical regions. In attempting to derive a better understanding of the causes of these changes from normal appearances it was decided to approach the subject by a study of the chests of a large number of individuals engaged in various dusty occupations. This work was instituted about a year ago on a small scale, but it soon proved to be of so much clinical and roentgenologic interest that it has been continued throughout the past year as time could be spared.

As a rule we have found firms and corporations quite willing to have the investigations carried out upon their employees, and it has frequently been to their advantage so to do, either by being assured that the dust inhaled by their men was not so harmful as was claimed, or by having ways and means suggested whereby the dangers from dust inhalations could be lessened. The Trenton Potteries Company and the Whitehall Cement Works have been most generous in supplying material and otherwise aiding us. A

number of carpet, plush and silk workers were furnished through the kindness of Dr. J. W. Schereschewsky, Surgeon, U. S. Public Health Service, and the remainder has been supplied through the Occupational Clinic of the University Hospital. Up to the present time one hundred and thirty-seven individuals have been examined, distributed through the following occupations:

ORGANIC DUST	
Carpet and plush workers	18
Tobacco workers	13
Silk workers	1
INORGANIC DUST	
Potters	39
Metal grinders	20
Cement workers	20
Asbestos workers	15
Coal miners and marine firemen	10
Not classified	1
Total	137

Each case has had a thorough clinical examination, followed by a roentgenoscopic study and a roentgenographic examination by stereoscopic plates. The clinical and roentgenologic studies have been made independently, and as this is in the nature of a preliminary report during the progress of our investigations, there has as yet been no comparison of the details brought out by the two methods of examination, except in a general way. It is obvious, therefore, that all minor details should be omitted from this report, and the results of our investigations at this time be limited to a statement of certain well-established general facts.

The entire subject is naturally to be regarded as a study of pneumoconiosis, a general term employed in referring to the effects induced in lung structure by the prolonged inhalation of abnormal quantities of dust. In a general study of the subject we have preferred to omit all reference to such terms as anthracosis, siderosis and chalicosis for the reason that they are indicative of the results of inhalation of certain kinds of dust, whereas many occupations imply the breathing of various forms, and the effects are the same in general but may vary in degree.

This report deals entirely with the roentgenologic aspect of the subject and is made at this time in an endeavor to aid in the more accurate roentgen diagnosis of pulmonary disease. The clinical and pathologic aspects of pneumoconiosis are by no means new, but thorough roentgenologic studies have been very few. Perhaps the most valuable contribution is to be found in *United States Health Bulletin* No. 85, issued January, 1917, comprising a clinical and roentgenologic study of 433 cases of "miner's consumption" among the zinc miners in Missouri, by Dr. A. J. Lanza, Surgeon of the U. S. Public Health Service, and Dr. Samuel B. Childs, of Denver. Another important contribution was made by Dr. W. W. Boardman in the June, 1917, issue of the *American Journal of Roentgenology*, dealing with cases of coal-dust inhalation and reviewing the roentgenologic literature on the subject.[1] Both of these were published while we were in the midst of our investigations, and it is interesting to note that the conclusions drawn by all of us, working independently, from the roentgenologic stand-point, have in the main been very much the same, differing only in minor details. Each of the above contributions has dealt with pneumoconiosis of a single origin, whereas we are endeavoring to study the condition as it arises from as many occupations as possible, and we have not, therefore, felt that our work conflicts with that of the other investigators. It has been proved by all that the roentgenogram, supplemented by a careful roentgenoscopic study, is by far the most accurate means of studying the effects of dust upon the lungs. The pathology of the disease has been well established by autopsy, and roentgen observations serve to accurately portray the exact conditions *in vivo*.

Practically all roentgenologists have had more or less opportunity to examine cases of pneumoconiosis, but most of these have been isolated examples of an advanced stage of the condition. In order to comprehend the various phases and to suspect and recognize them whenever seen and, most important, to differentiate the appearance of pneumoconiosis from those of other conditions,

[1] A third study of the effects of dust in gold miners has been published in South Africa. It has not been possible to obtain the original publication. An excellent abstract of the study can be found in the British Medical Journal, November 11, 1916.

particularly tuberculosis, one must make a systematic study of the roentgen pathology through all the stages and from the standpoint of every source of invasion. When one realizes the very numerous occupations that provide sufficient dust to induce changes in the lungs and the fact that dwellers in some large cities are subjected to sufficient dust to produce perceptible shadows in the lung structure it seems quite probable that errors in diagnosis must be frequent unless the possibility of pneumoconiosis be constantly borne in mind.

Three stages are to be recognized in the progress of the condition. In order to explain the condition itself and the changes which take place, brief reference must be made to the pathology, which is very simple. The first marked effect of excessive dust inhalation is irritation of the air passages which amounts to a chronic bronchitis. This in itself is responsible for more or less fibrous change which becomes legible in the roentgenogram as a thickening of the trunk shadows. This is no doubt also due to a certain amount of dust deposition in the cells and neighboring lymph structures. The thickened trunks and the lymphatic structures with increased density tend to increase the size and density of the hilus shadows. Added pigmentation of cells and increased depositions of dust particles in lymphatic structures farther out along the branching systems of the air passages gradually produce small areas of such density as to be visible and give to the lungs the characteristic mottled appearance so common in advanced cases of pneumoconiosis. Our experience has shown that this density is more or less closely related to that of the dust inhaled, being least in organic dust and greatest among metal grinders. Naturally the fibrous change that starts early from irritation increases, and there is later a decided fibrosis following up the deposition of dust. This seems finally to involve a large part of the lung structure and is no doubt responsible for the dyspnea by rendering the lung inelastic, which is readily determined by the lack of expansion noted by the fluoroscope, and particularly in the diaphragm. Bronchiectatic cavities are quite common in the late stages, and a similar process is manifest in the ultimate divisions of the passages as emphysema. The division of the process into three stages seems to be a foregone conclusion among those who have made a study of the subject. Before

any access to literature could possibly modify our views we had made practically the same classification which has been presented by the authors already referred to.

The first stage, roentgenologically speaking, is characterized by an increase in the hilus shadows and a thickening of the usually prominent trunk shadows, and an undue prominence of the finer linear markings. This is due to the causes just mentioned. It is the rule that the increase in thickness of bronchial trunk shadows is fairly uniform, which is the main dependence in distinguishing the case from one of peribronchial tuberculosis, but there are exceptions, and it is these which makes the roentgenologic diagnosis difficult or uncertain. Boardman aptly calls attention to the fact that roentgenologists have no doubt been mistaking early evidences of pneumoconiosis for tuberculosis. If the distribution of the thickening is irregular, as it frequently is, and the trunks to one apical region only are involved, the two conditions are quite difficult to distinguish by the inexperienced observer, and often almost impossible to differentiate by even the most experienced. A still more difficult problem is the detection of a peribronchial tuberculosis in the presence of evidences of the first stage of pneumoconiosis. In several instances we have recorded our plate readings as suspicious but we have not yet checked these up with the clinical findings. Abnormalities in the diaphragm excursion are to be included in all of the stages of the condition. We have certainly noted them in many instances in the first stage, contrary to the experience of Lanza and Childs. There is no general rule about them, however, in the first or even the second stages. When the excursion has been equally shallow on both sides in the first stage, we have frequently been unable to decide that this was not due to habit or to inability of many individuals of the laboring class to "show off" their diaphragms to best advantage. The position of the excursion during ordinary respiration between the limits of extreme inspiration and expiration is very variable. The most common finding was a restriction at the inner portion of the right diaphragm during full inspiration and either a decided flattening or a concavity of the outer aspect. It seemed as though the inner portion were halted in its descent by the process responsible for the thickened trunk shadows. It was our impression that

the descending trunk shadows were usually more thickened on the right side than on the left, but the interference offered by the cardiac shadow prevented a satisfactory proof of this supposition.

The second stage is characterized by a more or less uniformly arranged mottling throughout the lung structure due to depositions of dust in the lymph structures, cells, and fibrous tissue interspaces, with the addition of a certain amount of localized fibrosis. This stage comprises what has usually been regarded as the typical case of pneumoconiosis. Its onset seems to depend largely upon the *quality* of the dust inhaled. It occurs comparatively early in coal miners, cement workers and certain metal grinders, somewhat later in potters and asbestos workers, and quite late in those inhaling organic dusts. In regard to organic dusts, it may be stated here that they probably do not, of themselves, produce pathological changes in the lungs. When such changes do occur among those exposed to organic dust, they are to be ascribed to inorganic dust mixed with the organic. The volume of dust will, of course, enter into the statistics of this aspect of our work, and while this has been measured by Dr. Miller, comparisons have not yet been made. In metal grinders it was quite noticeable that mottling was observed before the usual first-stage appearances were well advanced. Cement, asbestos and carpet mills were the dustiest buildings examined by Dr. Miller, but no computations were made in coal miners. On the whole, it has been our experience that certainly quality and probably weight or density are more important factors in pneumoconiosis than quantity, contrary to the statement of Boardman. The *distribution* of the mottling is interesting. Invariably we have found it *first appearing* in the right lung, on a level with the hilus shadow, which is quite contrary to the statements of Lanza and Childs. It certainly becomes quite perceptible on the right side before it appears on the left, and for some time after it does begin on the left side, it is noticeably more marked on the right. Later on it is impossible to demonstrate any difference on the two sides. The distribution is more or less symmetrical, but naturally not uniform, throughout the lung. From the starting-point it gradually spreads to the bases and apices, but is never so marked at the extreme apices or bases as around the midportion of the lung. The *appearance* of the mottling depends more or less

upon the quality of the dust. In certain metal grinders the spots are very dense and sharply circumscribed and can be seen when very small. This is so to perhaps a less extent in coal miners, potters, and probably many other occupations. In cement and asbestos workers, among the inorganic dust occupations, the spots are noticeably softer and less sharply defined and the appearance is more like the early individual or conglomerate tubercle. In the organic dusts there is still further difference, probably due to admixture with very fine inorganic particles. Toward the end of the second stage the spots tend to enlarge and become conglomerate.

Errors in diagnosis are not so apt to occur in this stage. The appearance is so typical that no one is likely to mistake it for tuberculosis except possibly the miliary or bronchopneumonic types, and the history of the case is all that is necessary to correct any tendency to error. The distribution of the spots in the early stage and the comparatively slight amount of mottling in the apical regions later should put one on guard to ask questions. Here again, however, it may be exceedingly difficult to detect an early tuberculosis engrafted upon a well-advanced case of pneumoconiosis in the second stage. (See Figs. 1 and 2.)

The third stage is the most interesting period in this condition from the roentgenologic stand-point. It is characterized by the appearance of diffuse fibrosis and all that the term implies. As an end-result it does not differ greatly from the fibrosis that represents the terminal stage of chronic tuberculosis or some other less common causes. It is sometimes difficult to draw the line between the end of the second and the beginning of the third stage, and we are as yet uncertain as to the appearance at the period of transition. In some instances it would seem that the mottled appearance becomes more and more conglomerate and passes over into the appearance of dense fibrosis, sometimes closely resembling consolidation. In other instances a general haze seems to spread over a certain portion of lung, resembling a thickened pleura in a flat plate but resolving itself into lung structure in stereoscopic plates. The greatest density is in the subapical regions, although this is not the region of most intense mottling in the second state. We have imagined that the marked emphysema usually present at the bases must have some bearing upon this distribution. Dense fibrous

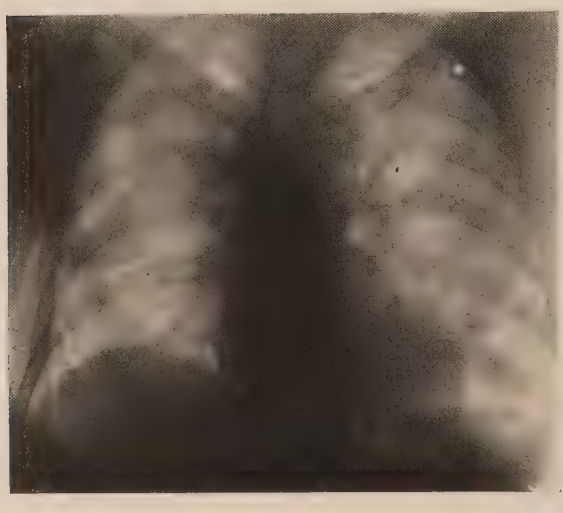

FIG. 1.—Chest of a coal miner who worked thirty-eight years *outside* the mines. Roentgenoscopic examination: No interference with diaphragm excursion. Stereoroentgenogram: Diffuse pneumoconiosis, with discrete spots, distributed from bases to apices. Fibrosis beginning in the right apex. There were no unusual chest symptoms. (Compare with Fig. 3.)

FIG. 2.—A case of old advanced and chronic pulmonary tuberculosis, with probably a recent exacerbation. Stereoroentgenogram: Pulmonary tuberculosis involving entire right lung, with evidences of infiltration throughout. The density would suggest an old or chronic process and most of it quiescent, with fibrosis.

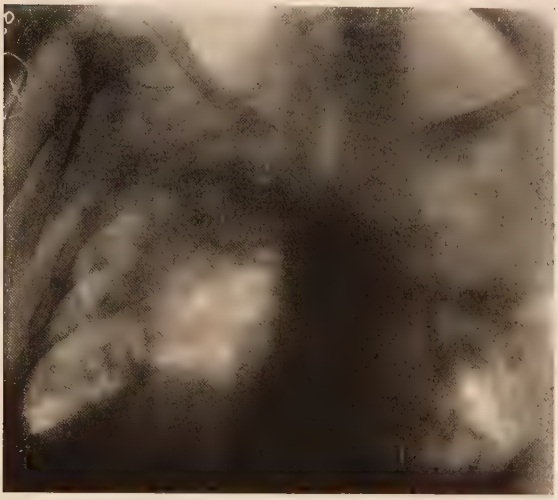

FIG. 3.—Extreme fibrosis in the chest of a coal miner who had worked *inside* a mine for thirty years. Stereoroentgenograms showed bronchiectasis and the fluoroscope showed no diaphragm movements. Repeated sputum examination negative for tubercle bacilli. (Compare with Fig. 1.)

FIG. 4.—Patient suffering from so-called "potter's asthma." Worked in a pottery for forty-five years. Extreme fibrosis, bronchiectasis, and absolute fixation of diaphragm. Marked dyspnea. He had previously been sent to a sanatorium for tuberculosis, but was discharged because of negative sputum. Repeated sputum examinations since roentgen studies were also negative.

bands can be seen extending in various directions, and frequently to the diaphragms, causing marked retractions. The heart and vessels are frequently dragged out of place. Bronchiectatic cavities are quite common. There is a very noticeable effect of inelastic lung structure upon respiration as studied by the fluoroscope. The ribs move little enough, and the diaphragms sometimes not at all. Is it in the least surprising that these unfortunate individuals suffer intensely from dyspnea? In this stage the mottling has become extremely coarse and sometimes is to be no longer recognized as such. (See Figs. 3 and 4.)

The differential diagnosis between the fibrosis resulting from tuberculosis and pneumoconiosis is frequently a most difficult problem, and we have had to acknowledge sometimes well-nigh impossible. It has been hard to believe that some individuals have not had tuberculosis, but repeated sputum examinations, sometimes over a number of years, have been negative. Still more difficult frequently is the detection of a tuberculosis engrafted upon this stage of pneumoconiosis. Suffice it to say that our studies have convinced us that errors in diagnosis have been made with considerable frequency.

DISCUSSION

Dr. Kober said the paper possessed, to his mind, not only extreme scientific interest, but was also of great economic importance. This must be apparent when we realize that in 1915 there were not less than 143,000 deaths from pulmonary tuberculosis in the United States, estimated upon the number of deaths actually reported in the registration area, more than one-half of those deaths occurred among industrial workers, who constitute only about one-third of the adult population. That fact seems to show a clear relationship between the undue prevalence of tuberculosis in the industrial worker and pneumoconiosis as a fundamental predisposing cause. He thought it could be safely said that persons exposed to the habitual inhalation of dust, sooner or later would develop some chronic inflammation of the respiratory organs, which may eventuate in tuberculosis. The quality of dust doubtless plays a more important role than the quantity, and the hard, sharp and angular fragments of steel and quartz dust appear to produce more intensive lesions than dust from coal, limestone, plaster of Paris and cement. A a matter of fact, workers in these

latter materials, although exposed to very intense volumes of dust, exhibit a certain degree of immunity from tuberculosis, the same being true of workers in sulphur. On the whole, however, statistics undoubtedly show, as pointed out by Sir Thomas Oliver that dust and fumes are the greatest foes of industrial life. For the solution of this economic problem we must look to preventive medicine, especially the department of industrial hygiene. The speaker was very glad to say that such expectations were not without hope of realization; because it has been shown by Professor Röpke that the tuberculosis death-rate at Solingen which is the seat of the cutlery industry in Germany, has been reduced from 540 per 100,000 population in 1885 to 180 in 1910. This gratifying reduction was largely the result of factory sanitation, especially the installation of exhaust ventilating devices calculated to remove the dust at the source of origin, and the compulsory use of these protective measures by the employees. Similar safety devices and ordinances exist at Sheffield, which is the seat of the cutlery industry in England; but the results have not been as favorable, possibly for lack of compulsory universal military training in England, laws on the statute-book are not always strictly enforced as they should be. The speaker is confident that whatever has been done in Germany can and will be done here, and anywhere, whenever the importance of the subject is appreciated, and the right kind of laws are enacted and strictly enforced.

Dr. Stockton said: A founder of this Association, Thomas F. Rochester, of Buffalo, forty years ago described "elevator pneumonia." The fact seems to have stepped out of literature of late years, and the speaker would again put it on record. Rochester described cases which at that time were seen in large numbers in Buffalo, which was distinctly an elevator city, in which the grain was lifted on old-fashioned lines. The men were exposed for many hours together to columns of dust, without any attempt at ventilation or protection; and during the rest of their hours they were badly housed and most unsanitary. We saw in those days many of these cases, and they were undoubtedly cases conformable to those described by Dr. Landis, except that here we had dust of various kinds, which he merely touched upon. However, the physical changes corresponded rather closely to those which we find in other forms of the disease, except that we had rather more acute processes, in the early part of the history. Later, the cases belonged to interstitial pneumonia, and occasionally tuberculosis, many times with asthma. These cases, which the speaker regards as fitly described "elevator pneumonia," still exist in the elevator district. He occasionally sees them presented at the clinic, and had shown them by *x*-ray representations, wherewith the second plate produced by Dr. Landis corresponded very closely.

Dr. Edsall said it had been shown in a considerable group of varieties of occupations in which there is a large exposure to dust, that there seems

to be a proneness, not only to chronic pulmonary affections, but a very decided proneness to acute pulmonary affections like pneumonia; and in some of those instances very severe mortality through pneumonia—at least he had had report of one such. One of the very extraordinary things about some of these dust exposures is, as Dr. Landis indicated, and what seemed to the speaker, the very long period of time through which people can be exposed to a very great deal of dust and apparently getting no definite effects from it. In some of those instances the same thing happens that he had seen an instance of at home. He had been asked to examine a plant and make some recommendation to the people; the plant was near his home, and which he had many times since seen; and he had never, in all his life, seen such extraordinary exposure to dust as there is in that plant. In the start, when he was going through it, not in relation to the dust condition but to a very peculiar nervous affection in consequence of the exposure to this ore dust, which they crush and then separate into the various components, he was asked to look at it because of their anxiety about this very extraordinary nervous affection, which he would not go into at this meeting, but which was a very peculiar thing. The dust conditions were perfectly amazing. In one part of it he passed as near as he in speaking stood to a post indicated, and was sure that he saw some object, and upon looking again realized that a man was there; but the dust was so thick he barely could make out that it was a man. Those men working in that frightful part of the plant have been working there for many years; the whole country around, for several hundred yards, is thickly covered with this dust; he knew for years, some of the doctors very well, exceedingly intelligent men, and was told by them that they have never been able to discover that there were any chronic effects from this dust. There may be some that they do not discover; he considers it very apparent that there are no very decided effects; but these physicians did tell him that there was a surprisingly large number of cases of pneumonia there, with a very high mortality; and he thinks that our observations in that connection are probably correct. In looking these workers over for this nervous affection, making a general physical examination of the men who had been profoundly affected nervously, he could find nothing in their lungs.

Dr. Landis, closing, stated that, like Dr. Edsall, he had not noted that any of the potters or cement workers that he had examined had been subjects of these acute infections. As to potters, his interest in them had been first aroused some four or five years ago, by having under his care a group of 25 of them, who had been sent to White Haven, supposedly for tuberculosis. Six of the 25 had the chronic type of fibrosis portrayed in his paper; and the other 19 had a mixed affection. The fibrosis probably would retard the disease rather than accelerate it. In fact, this has been noted by the English observers.

SUBACUTE AND CHRONIC NON-TUBERCULOUS PULMONARY INFECTIONS

By JAMES ALEXANDER MILLER, A.M., M.D.
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For a number of years I have been very much interested in a class of cases that have come under my observation from time to time, with very definite localized physical signs in the chest closely simulating pulmonary tuberculosis, the diagnosis of which disease has frequently been made, but in which a close study of the clinical findings and the subsequent course did not seem to justify this conclusion. When my attention was first directed to these cases the literature contained no references that I was able to find that seemed to fit in with their clinical aspect; but quite recently several American writers have described conditions which in some respects coincide entirely with mine, and which, taken together with my experience, appeared to furnish a basis for a distinct clinical entity. These cases have been variously described as "a lobar form of bronchopneumonia," "a localized subacute form of bronchopneumonia," and as "chronic non-tuberculous pulmonary infections."

Lord,[1] in 1902, and later in 1905, described in detail various infections of the respiratory tract due to influenza bacilli which were frequently confused with pulmonary tuberculosis. While most of his cases presented signs of disseminated bronchitis, or of localization at the pulmonary apices, two or three of them corresponded in their clinical features fairly well with some of those which I here present.

In 1913 Riesman[2] described a lobar form of bronchopneumonia of

long duration occurring in children and young adults. He reported 7 cases in detail, and stated that he had seen at least as many more.

Larrabee,[3] in 1915, reported 17 cases of which the characteristics were very similar to those described by Riesman. In both of these series the essential features were described as those of a subacute lobular pneumonia, with lobar distribution, occurring in one or the other of the lower lobes, usually of several weeks' or months' duration, sometimes with low fever, at others with no constitutional symptoms whatever, but tending gradually to complete recovery. No autopsies were reported. Larrabee reported roentgen-ray examinations in 6 cases, in 4 of which there were increased densities in the lower lobe, less intense and less circumscribed than in lobar pneumonia, and in the other 2 cases the roentgen-ray picture was normal. Neither of these observers systematically determined the character of the infecting organism, but both state that pneumococci predominated in the cases in which the sputum was examined. Both also found a very slight degree of leukocytosis in many of the cases which, however, was not constant. The cases reported by those two observers correspond to those which we will describe as a subacute type of non-tuberculous pulmonary infection.

Very recently Hamman and Wolman,[4] and after them Garvin, Lyall and Morita,[5] reported on a condition characterized by them as a chronic non-tuberculous pulmonary infection. The findings of these observers are very well in accord with each other and with some of the cases which will be here reported. In both of these studies great emphasis was placed upon the frequency with which these cases were confused with those of pulmonary tuberculosis. The characteristics were those of a chronic cough and expectoration, with periodic exacerbations, frequently with hemoptysis, extensive physical signs almost invariably affecting one of the lower lobes, and strikingly little impairment of the general health. Hamman and Wolman, from the physical signs and from the results in the 1 case which came to autopsy, described the pathology as a localized bronchitis with infiltration of the bronchial wall and foci of bronchopneumonia about the smaller bronchi. They stated that the infecting organism was most commonly the pneumococcus, less often the influenza, and still less frequently various types of

streptococci. Garvin and his associates studied the infecting organisms very carefully, and came to the conclusion that the influenza bacillus was the chief offender in the majority of their cases, being found in 7 out of the 8 cases reported, and predominating markedly in 4 of the 7. In 2 cases types of the streptococcus predominated.

The course of the disease is described as marked by extreme chronicity, the symptoms of which go on more or less continuously, but in which the intensity is varied by frequent remissions differing materially in their severity.

Garvin, Lyall and Morita lay stress upon the value of postural treatment in these cases, for the alleviation of the symptoms and also for intensifying the physical signs and obtaining specimens of sputum for actual bacteriological investigation.

The series of cases which I have to report, 22 in number, represent a portion of a considerably larger number which have been observed in the past few years. These particular cases are reported because of the facilities they have afforded for close study and not from any selection because of their special clinical features. They appear to fall into three distinct groups, which, however, fuse to a greater or less degree into each other, and which, when taken as a whole, and when also correlated with the reports of the observers already quoted, appear to form one distinct class of cases which deserves a place as a separate entity, and for which, employing an amplification of the designation suggested by Hamman and Wolman, the term "subacute and chronic pulmonary infections" seems justified. The cases will be considered under three groups: (1) the subacute type; (2) the subacute type with recurrences; (3) the chronic type.

Subacute Type. Nine of the 22 cases here reported are included in this type. These cases are characterized by a subacute onset often with coryza, but with marked cough and expectoration the predominating symptoms. The constitutional disturbance with fever is moderate and of short duration, usually two to four days, or may even be absent, after which the patient promptly regains the normal feeling of good health, but the cough and expectoration persist for several weeks or a few months. Hemoptysis may occur (Case I). There is no pain.

The physical signs are very characteristic and vary remarkably

little in the various cases. They are almost always confined to the whole or greater part of a lower lobe, and consist of slight dulness, somewhat impaired vesicular murmur, and subcrepitant and moist rales intensified by cough. In one case (Case V) the signs were at first over one entire lung, but later localized in the lower lobe. Sometimes, if seen early, a coryza may be present, and occasionally a few scattered sibilant rales may occur in other portions of the chest for a few days. Signs of pleurisy were found in 2 cases, in 1 of which (Case IX) there was a slight pleural effusion—the only one of the entire series.

The course of the disease in this type is a gradual disappearance of cough and expectoration, followed later by the complete loss of all physical signs, and ending in perfect recovery in a period varying from six weeks to four months.

Sputum Examination. The sputum is profuse and mucopurulent and persistently negative for tubercle bacilli. Cultures from the sputum were made in 8 of these cases and showed influenza bacilli in marked predominance in 5, pneumococci group IV in 2 and Streptococcus viridans in 1.

Roentgen-ray Examination. Roentgenograms were made in 7 cases; in 3 they were normal, in 3 others there was some intensification of pulmonary markings in the lower lobes, not necessarily most marked on the side of the lesion, and in 1 there was a slight pleural effusion.

Subacute Type with Recurrences. Six cases of the series are included in this type. These cases present the same clinical picture as those of the preceding type, run a similar course and apparently recover as they, but have been observed upon two or more separate occasions to have gone through the same cycle with an intervening period during which all signs and symptoms are absent. The striking observation during the recurrences is the fact that the physical signs reappear in the same portion of the lung as in the previous attack, giving basis for the assumption that the condition is a recurrence and not a new infection.

The symptoms, signs, and course of these cases, both in the original attack and the recurrence, are the same as before described. And this type also presents lesions always in one of the lower lobes.

Sputum Examination. Tubercle bacilli are uniformly absent. Cultures of the sputum were made in all 6 cases and in 3 of them in two separate exacerbations. Four of these cases originally showed pneumococcus type IV and 2 of them influenza bacillus. In the 3 cases in which later cultures were made during separate exacerbations, all of them originally showed pneumococcus type IV; on the second examination 1 of these again showed this organism, the second showed pneumococcus type II B, and the third influenza bacillus.

Roentgen-ray examinations were made in 5 of these cases and showed no abnormalities in 4 and slight intensification of the pulmonary markings in 1 at the site of the lesion.

Chronic Type. Seven cases of the series are here included. The distinction in type is made upon the fact that at no time while under observation have the abnormal signs disappeared, but, on the contrary, have remained fairly constant, although the predominating symptoms of cough and expectoration were subject to distinct exacerbations, so that symptomatically they closely resemble the former types.

In all essential features the signs and symptoms during the exacerbation correspond to those already described for the other types, but there exists a greater tendency to a more constant cough and occasional run of slight fever, and in two instances some tendencies to impairment of general health have been noted. In general, however, as in the previous instances, the general state of health and nutrition was maintained at practically a normal level. One case (Case XVI) has gone through a pregnancy uneventfully and is at the present time again pregnant in the seventh month and remains in good physical condition. In 4 cases pain in the affected side of the chest was a marked symptom.

One of these cases has been under observation seven years, another four years, and the others, with one exception, from two to three years.

Sputum Examinations. Tubercle bacilli were always absent in very numerous examinations. Cultures were taken usually during an exacerbation of the cough and expectoration in all 7 cases, and in 2 of them in two different exacerbations. Four showed pneumo-

cocci type IV, 3 of which showed the same on the second examination and the other influenza bacilli on the second. The other 3 cases showed Streptococcus viridans in predominating numbers.

Roentgen-ray examinations were made in 6 of these 7 cases. All showed abnormalities chiefly characterized by distinct accentuation of the pulmonary markings in one or both lower lobes, or as in 1 case throughout the entire lung. One showed a diffuse clouding as of pleuritic thickening, 2 irregularities of the diaphragm under the lesion, ascribed to adhesions, and in another the heart was displaced toward the side of the lesion, presumably by adhesions.

SUMMARY. *Sex.* When we consider the reports of all three types of this condition together we find that of the 22 cases 8 were males and 14 females. The predominance of females is probably a mere accident of no significance.

Age. The age incidence at the time of first observation varied from seven to sixty years, with the majority in full adult life, that is, from thirty to fifty years. The subacute cases, however, occurred with one exception before the age of thirty, and taking into consideration the probable incidence of the condition from the history of the other cases we find that the great majority had their first symptoms before the age of thirty-five. It is to be noted that of the 7 chronic cases, 4 began after the age of thirty, indicating that perhaps this type is more apt to occur in older persons, although this is not the case in Hamman and Wolman's cases nor in those reported by Garvin and his associates. From the experience of the subacute cases, and from several other cases in children which I have observed, but which are not here reported, I am inclined to agree with Riesman that when this condition occurs in younger persons prompt and complete recovery is the rule.

Seasonal Incidence. The time of year in which these infections occurred could be accurately determined only in the subacute cases. In the 15 cases of this type the original attacks occurred with much greater frequency during the colder months of the year. The date of the onset in 12 of these 15 cases was during the months from October to April inclusive. In the cases with recurrences 8 of such recurrences are reported, and 7 of these occurred also in this same period from October to April.

Site of the Lesion. The location of the physical signs was in the left lower lobe in 13 cases, in the right lower in 5, in both lower lobes in 3, and in the entire right lung in 1. In the cases of recurrence the signs returned in their original location excepting in one instance.

Cough and expectoration were the predominating features in all cases.

Pleurisy was not a frequent finding. Slight friction sounds were found in 2 cases and slight pleural effusion in 1 other. Three other patients complained of considerable pain in the chest on the side of the lesion, and these were all cases of the chronic type.

Hemoptysis. Frank hemoptysis occurred in 2 cases and bloody sputum at times in 4 others.

Bacteriological Findings. Very numerous and repeated examinations for tubercle bacilli were made in all cases, with negative results.

Specimens of sputum, obtained with particular care in order to get so far as possible the secretion from the lung uncontaminated with organisms from the upper air passages, were taken in all of the cases of the series excepting 1. These were studied both by direct smear and by cultures on various media. In a large number of cases also they were passed through white mice and smears and cultures were made by Dr. Avery in accordance with the technic developed at the Rockefeller Institute. The results of these cultures showed pneumococcus, type IV, predominating in 10 of the 21 cases, influenza bacilli in 8, and Streptococcus viridans in 3. In 3 cases of the series in which pneumococcus type IV predominated on the first examination the opportunity was offered for later cultures during a subsequent recurrence. In one of these pneumococcus type IV was again obtained; in another pneumococcus type II B in practically pure culture; and in the third the sputum during the second attack showed influenza bacilli in marked predominance. In many of the cultures comparatively few colonies of other organisms were present, such as Staphylococcus aureus and Streptococcus mucosus. Two of the cases in which the Streptococcus viridans predominated were cases of the chronic type.

Roentgen-ray Findings. Eighteen cases of the entire series were studied by means of the roentgen-rays. The most striking feature

of these photographs was the insignificant changes shown when compared with the extent of the physical signs. In 7 cases the plates were entirely normal, in 1 the plate was normal except for evidence of pleural effusion, in the 10 others the chief abnormality to be noted was an increase in density of the normal pulmonary markings, most marked in the lower lobes, but not necessarily confined to the affected side. These changes are similar to those noted in cases of chronic bronchitis or in chronic pulmonary congestion secondary to cardiac disease. They in no way whatever have any resemblance to the picture shown by tuberculous infiltration which is in striking contrast to the physical signs which closely resemble each other in these two conditions.

In 4 of this last group of cases there was in addition to the intensified markings some evidence of pleuritic adhesions. These 4 cases were all of the chronic type.

It is to be noted that all of the chronic cases examined by the roentgen-rays showed some change, while in the subacute types, whether with or without recurrences, the majority of cases were normal upon roentgen-ray examination.

Discussion. There is a striking similarity between these three types of cases. The clinical picture of the original attack coincides in every respect with that later found either in the recurrence of the infection or in the exacerbation of the chronic case. The symptoms, the physical signs, the site of the lesion as well as the bacteriological and roentgen-ray findings do not materially differ. The differences are principally in the further course of the disease, that it may clear up more or less promptly or may recur after an interval of months or more, or, lastly, may continue as a constant chronic condition marked by periods of exacerbation.

In the subacute type it is easy to recognize the same condition which was described by Riesman and Larrabee. In the chronic type we have all of the essential features of the cases reported by Hamman and Wolman and by Garvin, Lyall and Morita. The subacute type with recurrences is the link between the two. It seems quite evident that in all three types we are dealing with the same disease. It would appear probable that, as further opportunity to watch the subacute cases is afforded, many of them may

recur, and that of these not a few may drift into the chronic type, for already one or two of the cases which have evidenced several recurrences show a tendency to a longer persistence of physical signs in the later attacks.

The pathological basis of the condition is incomplete, for the disease is not a severe or fatal one. The only available postmortem findings are those of the case reported by Hamman and Wolman, which showed the bronchi of both lower lobes dilated and filled with pus, with areas of bronchopneumonia about them. Both Riesman and Larrabee considered the condition to be one of subacute bronchopneumonia.

The evidence which we have to offer from the roentgen-rays does not indicate that there could be very much actual pneumonia in these cases, and this is in harmony with the absence of the physical signs of consolidation.

With due regard to the hazards attending the interpretation of slight variations from the normal roentgen-ray picture of the lung it is at least suggestive that the intensification of pulmonary markings occurred most uniformly in the chronic cases, and that in these evidences of pleural involvement by adhesions were presented. It was in these cases only that pain was a marked symptom.

It is suggested that the pathology of the condition may consist of a localized bronchitis with lobar distribution involving the submucous and peribronchial tissues of the bronchi. This may clear up or persist in a latent subacute form, offering a site predisposed to the recurrence which in turn increases the tendency to the production of fibrous tissue. This is the permanent condition in the chronic type, and with it may be associated a bronchopneumonia, the occurrence of which may explain the periodic exacerbations with fever. This corresponds closely to the pathological conception of the condition expressed by Hamman and Wolman.

It seems very probable that some of these cases may later develop into chronic interstitial pneumonia or bronchiectasis, although I have never personally observed such a development.

Considering the nature of the bacterial infection our findings are in harmony with the reports of the other observers as to the pre-

dominating organisms cultured from the sputum. As already stated, Riesman, Larrabee and Hamman and Wolman all laid stress upon the pneumococcus as probably the important infecting agent, with influenza of secondary importance. Garvin, Lyall and Morita, however, found the Bacillus influenza the predominant infection in their chronic cases. As in our observations in the chronic type they also found varieties of streptococcus playing a part in some of their cases.

The higher percentage of predominating pneumococcus cultures found in our series may be due to the fact that it includes a large proportion of subacute cases, the bacteriology of which may differ from that occurring in the chronic forms studied by Garvin, Lyall and Morita.

The reappearance of physical signs in the same portion of the lung in different recurrences raises the question as to whether these recurrences are due to new infection from without or to recrudescences of the same infection which may lie dormant in the lung. That it may be a new infection is suggested by the fact that in 2 of our cases observed in separate attacks, organisms were found which differed from those first obtained. In order to throw light upon this phase of the problem in a number of pneumococcus cultures which were passed through mice the spleens of the animals were sealed and preserved in the hope that during a second attack the opportunity might be offered to compare the reaction of the two cultures to immune sera. Unfortunately for our object such recurrences in these particular cases have not occurred.

Another interesting feature is the fact that 4 of our cases occurred in pairs, 2 each in the same family, 1 case following the other, so that the probability of communication of the infection between them is very great. In the first pair the organism recovered from the culture was influenza bacillus in almost pure culture. In the second instance both influenza and pneumococcus type IV were recovered. In the original case of this pair the pneumococcus type IV predominated, in the secondary case the influenza predominated. At the time the cultures were taken the first case had already passed the acute stage, which may have influenced the results of the sputum cultures.

Differential Diagnosis from Pulmonary Tuberculosis. That this condition offers many points of similarity to pulmonary tuberculosis is evident. The practical demonstration of this is afforded by the fact that very many of them first came under observation after having been diagnosed as tuberculous by competent observers. The chief points which serve to distinguish them from tuberculosis may be summarized as follows:

1. Complete absence of severe constitutional symptoms with the retention of excellent general condition in spite of the presence of extensive lesion.

2. The localization of the lesion with almost constant uniformity in one or both of the lower lobes.

3. The disappearance of all physical signs within a few months in the subacute cases.

4. The lack of progression of the lesion from its original site to other parts of the lungs.

5. The absence of tubercle bacilli in the sputum over long periods of time and the presence of other infectious organisms in predominating numbers.

6. The character of the roentgen-ray picture, which in these cases shows either nothing abnormal or very slight changes.

I wish to acknowledge my deep obligation to Dr. Oswald T. Avery not only for his great courtesy in making many painstaking bacteriological examinations, but also for his valuable advice upon many problems arising in the course of this study.

SUBACUTE TYPE

Case I.—A. G., male, aged twenty-two years; first seen August 1, 1913.

Previous History. The patient has not been subject to colds. He has been well excepting in the past year, when he had pain and vomiting and other digestive symptoms, for which a diagnosis of ulcer of the stomach had been made.

Present History. Four weeks previously, after rather hard exercise, he felt feverish, developed a slight cough, and his temperature was at 100° or 101° for ten days. He had no pain. Since then he has run a slight temperature, 99° or 99.5°. Two days previously he had had a distinct hemoptysis, about 3 drams. A diagnosis of pulmonary tuberculosis had been made by his physician.

Physical examination showed a slight dulness over the right lower lobe, with diminished breath sounds and numerous moist rales.

Course of the Disease. August 20 these signs were markedly diminished and the cough and expectoration much less. When seen on November 18, they had entirely disappeared. When last seen, January 1, 1914, the patient was in ordinary health and had resumed his normal occupation. There were no signs in the chest. His physician reported (1917) that he has continued perfectly well ever since.

Sputum culture showed influenza bacilli in almost pure culture.

Roentgen-ray examination was not made.

Case II.—G. (brother of Case I) aged twenty-four years; first seen August 1, 1913.

Present History. The patient had had a cold in the head, cough and expectoration for ten days, with no fever, and he had kept at his ordinary occupation. The cough and expectoration were marked.

Physical examination showed numerous moist rales over the left lower lobe.

Course of the Disease. The symptoms subsided in two weeks. No opportunity for further examination was offered. His physician reported (1917) that he has had no further symptoms referable to his chest.

Sputum examination showed influenza bacilli in almost pure culture.

Note. A domestic in the same household as these 2 cases was sick with la grippe and bronchitis at the same time. Opportunity was not offered to examine her.

Case III.—J. F., female, aged twenty-three years; first seen December 18, 1916.

Previous History. The patient had been subject to colds and cough in the winter, but they were never serious.

Present History. She had a cold in the head which began in October, 1915, and a cough developed a month later. Cough and slight expectoration had persisted ever since. Three days before she was first seen she had a slight fever and soreness in the left chest. There had been slight loss of weight and some malaise for the past month, but the patient had kept at her work regularly. She thought she might have had a little fever during the past few days. A diagnosis of pulmonary tuberculosis had been made.

Physical Examination. Normal percussion note; slightly diminished breath sounds with fine subcrepitant rales over the entire left lower lobe.

Course of the Disease. The patient was kept quiet in the open air for a week, at the end of which time the symptoms were less, although the signs persisted. She went away to the country for three weeks and then came back feeling perfectly well. She was last examined January 29, 1917, when the signs had entirely cleared up excepting for a few rales at the extreme left base. The patient has been well and at work ever since, with no symptoms.

Sputum examinations were persistently negative for tubercle bacilli. Cultures were not made.

Roentgen-ray examination, December 19, 1916, showed peribronchial thickening in the lower lobe, most marked on the right side.

CASE IV.—I. G., male, aged forty-five years; first seen December 15, 1915.

Previous History. The patient had always been well.

Present History. Five weeks previously the patient had developed a cough, with expectoration, without fever, and without any constitutional symptoms. He had kept at work regularly. A diagnosis of tuberculosis had been made.

Physical Examination. Over the entire right lower lobe there was slight dulness, diminished breath sounds, and numerous subcrepitant rales.

Course of the Disease. The patient went to Lakewood and led an open-air life. Three weeks later, on his return, he was much improved. The cough and expectoration had disappeared. The signs were then confined to a small area at the extreme right base. He has not been seen since.

Sputum examinations have always been negative for tubercle bacilli. Culture (Dr. Avery) taken January 4, 1916, showed influenzæ and pneumococci type IV, influenzæ predominating.

Roentgen-ray examination, December 15, 1915, showed slight peribronchial thickening in both lower lobes particularly on the right side.

CASE V.—W. V., male, aged sixteen years; first seen October 3, 1916.

Previous History. The patient had always been subject to colds.

Present History. In August, 1916, he contracted a cold, beginning with coryza, and since then has had cough and expectoration. There has been no fever or night-sweats or loss of weight; excepting for the cough and expectoration, the patient feels perfectly well, but had been told that he had tuberculosis.

Physical examination showed numerous subcrepitant rales over the entire right chest, most marked over the right lower lobe but also heard over the upper lobe. There was slight diminution of vesicular murmur and very slight dulness at the extreme right base.

Course of the Disease. The patient was kept quiet in the open air in Lakewood, and on his return, November 13, the signs in the chest had disappeared except in the right lower lobe, where there were scattered subcrepitant rales. December 19 the patient reported that the cough and expectoration had entirely disappeared several weeks previously, and on physical examination the signs in the chest had also disappeared. Since that time the patient has been entirely well.

Sputum examinations were negative for tubercle bacilli on two occasions. Culture showed Streptococcus viridans predominating, with few Staphylococcus aureus.

Roentgen-ray examination, October 3, 1916, showed a slight increase of the pulmonary markings throughout the right lung, more marked in the lower lobe.

Roentgen-ray examination, December 19, 1916, showed still somewhat increased pulmonary markings in the right lung, but less marked than previously.

Case VI.—M. M., male, aged thirty years; first seen November 27, 1915.

Previous History. He had had a syphilitic infection two years previously and one very protracted cold, with bronchitis, eighteen months previously. He had kept at his usual work.

Present History. For one month he has had a cough, with marked expectoration, which began with a coryza. There were no other symptoms.

Physical examination showed very numerous moist rales over both lower lobes, more marked on the left side, with a few sibilant rales in the rest of the chest; also an acute coryza.

Course of the Disease. The patient was put in bed for ten days. He had no fever. The cough and expectoration gradually diminished, and on December 6 the signs in the right chest had entirely disappeared, but there were localized rales and slight dulness over the entire left lower lobe. After that he went to the country. He was last seen on March 1, 1916, when the chest was entirely clear.

Wassermann test was made December 18, 1915, +++. At that time he was put on specific treatment. The signs in the chest had already begun to disappear.

Sputum examinations were persistently negative for tubercle bacilli. Culture December 6, 1915, showed pneumococcus type IV predominating, with some Staphylococcus aureus.

Roentgen-ray examination, November 27, 1915, showed nothing abnormal in the lungs.

Case VII.—M. C., female, aged seven years; first seen February 29, 1916.

Previous History. In October, 1915, she began with a cough which developed into whooping-cough, which gradually subsided and the child returned to school the first week in January.

Present History. January 15 she again began to cough severely and raised considerable quantities of sputum. These symptoms continued up to the time of the examination and the child seemed pale and a little languid, but apparently had no fever.

Physical examination showed normal breath sounds in the left lower lobe, with numerous subcrepitant rales. Scattered over the upper left lobe and the entire right chest there were sibilant rales, with a few fine subcrepitant rales at the right base.

Course of the Disease. March 7, 1916, these signs had entirely disappeared excepting for localized rales over the lower three inches of the left

posterior chest, with somewhat diminished breathing. March 7 these signs had entirely disappeared. The patient in the meantime had lost the cough and was feeling and acting well.

Sputum examination (Dr. Avery) March 1, 1916, culture showed influenza markedly predominating; a few Streptococci mucosus.

Roentgen-ray examination, February 29, 1916, showed enlarged glands at the root of the lung on the right side; slight infiltration extending inward from this into the parenchyma; bases normal.

Case VIII.—I. L., female, aged twenty-one years; first seen April 2, 1917.

Previous History. Right apical tuberculosis discovered in October, 1915. The patient had been at Stony Wold Sanatorium for ten months, and since that time had been at home. She had not gone back to work but had been feeling perfectly well for some time.

Present History. Three weeks ago she had had what she thought was la grippe. She was confined to bed with fever and a bad cough with expectoration for a week. Since then the cough and expectoration have been very marked and have continued up to the present time. She was seen by the physician who had previously treated her for tuberculosis, and was told that she had an acute tuberculosis of the left lower lobe, and artificial pneumothorax was advised.

Physical Examination. There was marked dulness and marked vesicular breathing; numerous moist rales over the entire left lower lobe. A few friction sounds at the axilla. There was slight dulness and prolonged high-pitched breathing at the right apex.

Course of the Disease. The patient is still under observation. The physical signs are the same. The cough and expectoration are very much less. The patient already feels perfectly well and wants to return to work.

Sputum examination was negative for tubercle bacilli. Culture (Dr. Avery) showed pneumococcus type IV predominating with some influenza.

Roentgen-ray examination, April 2, 1917, showed a few calcified tubercle bacilli at the right hilus and up toward the right apex. The lower lobes of both lungs were absolutely normal.

Case IX.—J. L., female, aged twenty years; first seen April 17, 1917. (This patient is a sister of Case VIII; she is particularly interesting because she was taken ill shortly after her sister with very similar symptoms.)

Previous History. Patient had always been well; not subject to coughs and colds.

Present History. Ten days previously she went to bed feeling chilly and feverish and with a sharp cough. There was no coryza. She stayed in bed with considerable cough, but no expectoration, for a week. For the past three days she has been feeling very much better. The cough has continued, with some expectoration. The patient is now up and about. There was no pain in the chest.

Physical Examination. Over the entire left lower lobe there is dulness merging to flatness at the base, with an area of distinct bronchial and voice sounds at the left axilla. Above this area and extending upward two inches above the angle of the scapula, the breath sounds were somewhat diminished, and there were numerous crepitant and subcrepitant rales. The chest was explored and a few cubic centimeters of slightly cloudy pale serum were obtained. On examination this fluid was sterile. Differential cell count showed large mononuclears 63 per cent., small mononuclears 27 per cent., polymorphonuclears 9 per cent.

Leukocytes 13,800, polymorphonuclears 75 per cent.

Course of the Disease. The patient improved rapidly, and when last seen, April 26, although still coughing and expectorating, she was feeling in good general condition and the signs of fluid in the chest had entirely disappeared. The subcrepitant rales over the entire lower lobe still persisted.

Sputum examination was negative for tubercle bacilli. Culture (Dr. Avery) showed the original smear crowded with influenza bacilli, with a few pneumococci type IV. After passage through a mouse the influenza bacilli were still in very large quantities, with also a few pneumococci type IV.

Roentgen-ray examination showed a dense shadow at the left base, homogeneous in character, due to fluid, with slight increase of the pulmonary markings above the level of the fluid. There is a large calcified tubercle at the root of the right lung.

SUBACUTE TYPE WITH RECURRENCES

Case X.—R. C., female, aged sixty years; first seen for this condition November 15, 1915.

Previous History. The patient has been under my observation for ten years suffering from arteriosclerosis and valvular heart disease.

Present History. November 13, 1915, she had coryza with slight fever. November 15 she was not feeling very sick and not confined entirely to bed. Her temperature was 99° and she complained of considerable spasmodic cough and expectoration.

The patient gave a history of having had a similar attack to the present one in April, 1915, while South, which lasted about a week. Communication with the physician in charge showed that he had made a diagnosis of a slight pneumonia in the right lower lobe which quickly cleared up.

Physical Examination. In the right lower lobe there was marked dulness, diminished breath sounds, and numerous moist rales.

Course of the Disease. For three days the temperature ran between 99° and 101° with continuation of the symptoms and very little constitutional

symptoms. On November 17 there was a hemoptysis, about 1 dram. In five days the temperature was normal and remained so. December 20 the lungs were entirely clear.

The patient kept in ordinary health, with no signs in the chest until November, 1916, when she came in complaining of cough and expectoration which had begun two weeks previously, with no constitutional symptoms. There were a few rales at the right base. The patient took a long automobile drive and on returning home had fever to 101° and marked increase of cough and thick, purulent expectoration. The signs at the right lower lobe were much more marked. The temperature subsided in three days; the cough and expectoration disappeared in a week. When the patient was last seen December 21, 1916, there were a few fine rales at the right base.

Sputum culture (Dr. Avery) in the first attack, November 16, 1915, showed a pneumococcus type IV in almost pure culture. In the second attack, December 8, 1916, it showed pneumococcus II B in marked predominance with almost no other organisms.

Roentgen-ray examination was not made.

Case XI.—Mrs. C. D., aged thirty-four years; first seen March 11, 1916.

Previous History. Three years ago she had la grippe and bronchitis. In November, 1915, the patient had pneumonia which came on gradually with malaise for three days before going to bed. She had cough and expectoration and fever which lasted for about a week. She was in bed for three weeks. A report from her physician states that there was then consolidation of the entire left lung, which cleared up in the upper lobe but not entirely in the lower. When he last saw her, December 11, there were still signs in the left lower lobe similar to those present when she first came for examination, March 11, 1916.

Present History. Since the attack of pneumonia she has had considerable cough, which is worse at some times than at others. For the past month following a cold in the head this has been particularly bad. There has been no pain. The patient is three months pregnant and consequently rather miserable.

Physical Examination. There is dulness over the left lower lobe, bronchovesicular breathing, and very moist consonating rales. The heart shows definite signs of mitral stenosis and aortic insufficiency.

Course of the Disease. The patient was put at rest and the termination of pregnancy was seriously considered. March 27, however, when last seen, she was very markedly improved and the signs in the chest were very much less. The pregnancy was allowed to go on. She has not been seen since.

Sputum Examination. Several examinations of sputum were negative for tubercle bacilli. Culture (Dr. Avery) showed influenza in marked predominance in all of three separate specimens.

Puncture of the lung showed no growth.

Roentgen-ray examination, March 17, 1916, showed very slight increased density in the left lower lobe, peribronchial in character.

Case XII.—J. S., female, aged thirty years; first seen September 28, 1915.

Previous History. The patient had pneumonia four years ago, reported by the physician in attendance to have been in the left lower lobe. She made a good recovery and was never very ill. Otherwise she had always been well and strong.

Present History. Eight days previously she had a gradual onset of cough and expectoration, slight fever, 100° to 101°, no pain. She had not been confined to bed and had very few constitutional symptoms. Her chief complaints were marked cough and expectoration. A diagnosis of acute pulmonary tuberculosis had been made.

Physical Examination. There was distinct dulness over the entire left lower lobe, some diminished respiratory murmur, and numerous rather large moist rales.

Course of the Disease. She was put to bed and kept there for two weeks. The symptoms gradually subsided. She was next seen October 29, 1915. The cough and expectoration had then entirely disappeared. The physical signs showed very few subcrepitant rales in the lower left axilla and extreme left base. December 1, 1915, examination of the chest showed it entirely normal, and since that time the patient has been perfectly well.

Sputum examination, October 1, 1915, showed pneumococci type IV markedly predominant with a few Staphylococci aureus.

Roentgen-ray examination, October 29, 1915, showed no abnormalities excepting slight increase in hilus shadows.

Case XIII.—L. C., male, aged thirty-two years; first seen March 22, 1916.

Previous History. The patient had always been well until one year previously when he began to cough, with some expectoration, especially in the morning; he had had slight malaise with some fever; he had been working regularly.

Present History. The past week he has had exacerbation of symptoms, with marked increase of cough and expectoration, and a diagnosis of tuberculosis had been made.

Physical Examination. Below the angle of the right scapula to the base there was a slight dulness, normal vesicular breathing, and numerous subcrepitant rales.

Course of the Disease. March 28 the symptoms were somewhat less marked, but the signs persisted as before. He was next seen April 21, 1917. He stated that he had been perfectly well until October, 1916, when he developed a cold in the head followed by marked cough and expectoration,

which continued until February, 1917. His general condition was perfectly good and he continued at work regularly. Since February there has been no cough or expectoration. There were no signs in the chest in April, 1917.

Sputum culture March 22, 1916 (Dr. Avery), showed influenza in enormous numbers in pure culture.

Lung puncture showed no growth.

Roentgen-ray examination, March 22, 1916, showed nothing abnormal.

Case XIV.—R. McC., male, aged fourteen years; first seen in July, 1914.

Present History. The boy had a cough which had lasted three months. He was an athlete accustomed to hard physical exercise which he had continued to take. The expectoration had recently gotten less, but there was still a good deal of cough. There was no definite interference with the general health.

Physical Examination. In the left lower lobe posteriorly there was dulness, diminished vesicular breathing, and fine subcrepitant rales most marked on coughing.

Course of the Disease. The patient was made to rest in the country and his cough gradually improved; after four months it had almost disappeared. The signs also improved, but a few rales still persisted.

Two months later he caught a fresh cold and for a couple of days had a little fever, with marked increase of cough and expectoration. During this time the rales appeared even more numerous than when first seen. They gradually diminished after three or four weeks, but never entirely disappeared. He was taken out of regular school and sent to California, where he spent a year in the open air, during which time he was perfectly well. When he returned to New York the signs in his chest were limited to very few rales just below the angle of the left scapula. The next winter, while at his home in the country, he had another fresh cold, with recurrence of cough and expectoration and return of the rales over the same area of the chest. These persisted three or four weeks and then gradually disappeared. During the past two years the boy has been in excellent physical condition, has had no colds or cough, and on last examination there were no signs heard in the chest.

Sputum examinations were always negative for tubercle bacilli. Culture (Dr. Avery) showed pneumococcus type IV in marked predominance in two separate exacerbations.

Roentgen-ray examination, July 13, 1916, showed nothing abnormal. December 15, 1916, showed nothing abnormal.

Case XV.—L. C., female, aged thirty-five years; first seen December 3, 1915.

Previous History. Eight years ago the patient was run down and had a slight cough. A diagnosis of tuberculosis was made. She was under a

physician's care for four years, never very sick. She was told that the trouble was in the lower part of the right lung. Since then she has had occasional wheezing in the chest, but no other symptoms until the present attack.

Present History. Two weeks ago she began to cough, with a moderate amount of thick, yellow expectoration. She had occasional slight fever, no pain, no night-sweats. She kept at work as a stenographer.

Physical Examination. Over the entire right lower lobe there is slightly impaired resonance, slightly diminished breath sounds, with numerous subcrepitant rales, heard especially on coughing.

Course of the Disease. She stopped work and was kept under observation. The signs gradually diminished until in a month they had almost entirely disappeared. March 10, 1916, she returned for examination, with a history of having been perfectly well, without cough until one week previously, when she had a coryza and a return of cough, expectoration, and slight fever, about 100°. She had kept at work. Examination showed a few rales at the right base, numerous moist and consonating rales over the left lower lobe, with slight dulness.

N. B.—This is the only case in which the recurrence appeared in the opposite side from the original lesion.

Sputum examinations were persistently negative for tubercle bacilli. Culture showed pneumococci type IV predominating and a few Staphylococci mucosus.

Roentgen-ray examination, December 3, 1915, showed thickening at the roots of both lungs with enlarged bronchial glands. No abnormalities in the parenchyma and absolutely no increased shadows at the right base.

CHRONIC TYPE

Case XVI.—Y. S., female, aged thirty-three years; first seen May 27, 1914.

Previous History. The patient had always been perfectly well until two years ago, when she gradually developed a cough and pain in the left posterior chest. At that time a diagnosis of tuberculosis was made. The patient went to the country for a few months and the symptoms entirely subsided.

Present History. A few months ago she began to have pain again in the left chest posteriorly and slight cough. She was in good general condition and was seven months pregnant.

Physical examination showed slight dulness, normal breath sounds and fine subcrepitant rales from one inch above the angle of the left scapula to the base.

Course of the Disease. The patient went to the country for a few weeks and improved a good deal. She went through her confinement normally

and was next seen November 14, 1914. She was complaining of a return of a slight cough and expectoration, which at times was bloody. She was at that time nursing her child. The physical examination revealed the same signs as previously. She was advised to stop nursing and take more rest. She improved and lost her cough and kept in good health in every way, until April, 1916, when she returned again complaining of pain in her left chest but no cough. The physical signs were exactly the same as before. She was advised to give up some of her hard housework at home. She stayed in New York and kept in very good condition in every way, and had no symptoms at all until January, 1917, when she began to cough and expectorate. She had no fever and felt generally very well. The cough subsided in a few weeks, but a very marked, thick, purulent expectoration continued and the pain in the left scapular region returned. She continued to work hard at her housework at home. She again reported for examination on April 19, 1917, when the physical signs were found to be the same as before excepting that the rales extended a little farther upward than previously.

Sputum examination was negative for tubercle bacilli on several examinations both in 1914 and 1916.

Culture, April 19, 1917, showed pneumococci type IV predominating with few Staphylococci aureus.

Roentgen-ray examination, April 23, 1917, showed slight increased density of the pulmonary markings in both lower lobes.

Case XVII.—R. S., female, aged forty-two years; first seen June 30, 1910.

Previous History. The patient gave a history of pain in the left side, with cough and expectoration sometimes streaked with blood, three years previously. After several months a diagnosis of pulmonary tuberculosis was made and the patient spent nearly a year at Stony Wold Sanatorium.

Present History. At the time she came for examination she still had a little cough, no expectoration. She felt rather weak, although her weight and general nutrition were normal.

Physical Examination. There was a slight dulness; normal breath sounds, numerous moist rales from the angle of the left scapula to the base.

Course of the Disease. She was observed for about three months, during which time she had no fever; she felt rather weak and complained of pains in the left chest. There was very little cough. She then went to a sanatorium at Bedford Station, where she stayed about four months. She gained weight and her general condition improved. She was next seen March 16, 1911, when the physical signs were the same as before. Since that time she has been seen at regular intervals, and on every occasion the physical signs have persisted as at first. At times there would be a little exacerbation of the symptoms, with slight cough and occasional slight fever, 99° to 100°. The pain in her left shoulder-blade has always been a

marked symptom. During this time her general condition has failed somewhat, and when last examined, April 19, 1917, she felt weak and dragged out, had considerable pain in her left shoulder-blade and very slight morning expectoration. The physical signs remained the same as before. Her weight is only a few pounds less than when first seen in 1910.

Sputum examinations for tubercle bacilli were made frequently during all these years, and always with negative results. Culture (Dr. Avery) March 15, 1916, showed pneumococcus type IV predominating. Culture April 20, 1917, showed pneumococcus type IV markedly predominating.

Lung puncture at that time showed no growth.

Tuberculosis complement-fixation test was negative.

Roentgen-ray examination (Dr. Hirsch) April 20, 1917, showed diffuse intensification of lung markings throughout both lungs. The left diaphragm was high and irregular as by adhesions.

Case XVIII.—P. L., female, aged thirty-five years; first seen November 19, 1913.

Previous History. Had always been well.

Present History. Nine months previously she contracted a cold in the head and cough. The cough had persisted ever since, worse sometimes than at others. She thought she had had slight fever at times, but had kept at work regularly.

Physical examination showed localized subcrepitant rales below the angle of the left scapula. No abnormalities on percussion and in breath sounds.

Course of the Disease. The patient has been kept constantly under observation since that time. She has had recurrent exacerbations, sometimes with coryza and always with increased cough and expectoration. The signs have usually been slight. In March, 1914, there was a more acute attack with dulness, diminished breath sounds and very numerous moist rales over the entire lower lobe. No fever. One month later the signs had returned to their former extent.

Examination on January 1, 1915, showed the chest almost entirely clear.

She was seen on December 18, 1916. She had been very well, working regularly and was in good physical condition. Has had a few coughs and colds off and on. For the past few days she had a slight increase of cough and wheezing in the chest. On examination the rales over the left lower lobe were present over a small area below the angle of the scapula. When last seen, January 19, 1917, these signs were distinctly less.

Sputum examinations for tubercle bacilli were always negative. Culture, March 25, 1914, during a more acute attack, showed pneumococcus type IV predominating; few streptococci. Culture December 18, 1916 (Dr. Avery) showed influenza markedly predominating.

Roentgen-ray examination was not made.

Case XIX.—Mrs. H. K., aged thirty years; first seen November 8, 1917.

Previous History. Pneumonia at fourteen, pleurisy several times, always on the right side. The last attack was one year ago. She had always been subject to colds and cough but her general health had never been affected.

Present Illness. On September 18, 1916, she had a bad cold in the head which was soon followed by marked cough and expectoration. Temperature was 99° to 100.5°. Since that time she has continued to cough and expectorate, but has had no fever. She is now six weeks pregnant, and had been told that she had tuberculosis.

Physical examination showed slight dulness, diminished breath sounds, with numerous moist rales over the entire right lower lobe.

Course of the Disease. It was recommended that the uterus be emptied and that the patient go to the country and rest. This was done. The patient returned with very much less cough and expectoration. When she was next seen on December 15, she was very much improved but still had a cough and expectoration which was occasionally blood-streaked. The signs in the chest had not changed.

The patient has been seen off and on ever since and has been doing extremely well so far as symptoms are concerned. When she was last seen March 17, 1917, she had no cough or expectoration for several weeks; the signs in the right lower lobe persisted but were distinctly less marked.

Sputum examinations were persistently negative for tubercle bacilli. Culture, November 9, 1916 (Dr. Avery) showed influenza predominating with few Streptococci hemolyticus, and few pneumococci type IV.

Roentgen-ray examination, December 15, 1916, showed increased densities in both lower lobes, particularly on the right side where the clouding was rather diffuse, suggesting pleural thickening.

Case XX.—H. F., male, aged forty-one years; first seen September 18, 1914.

Previous History. The patient had pneumonia nineteen years ago. Since that time he has been rather subject to colds and coughs but in good general condition.

Present History. Two years ago he was examined by a specialist in Montreal and told that he had tuberculosis in the lower lobe of the left lung. He rested for a month. Since that time he has been working regularly. He has had some pain in the left side which has been a little more marked of late, for which symptom he comes for examination.

Physical Examination. Over the entire left lower lobe there was a slight dulness, diminished vesicular breathing and numerous fine, subcrepitant rales intensified by coughing. The patient was in good physical condition, had a normal weight, no fever or other constitutional symptoms; no cough or expectoration.

Course of the Disease. The patient has been under periodic observation up to the present time at intervals varying from six months to a year. He has had a slight cough and expectoration without coryza or constitutional symptoms, associated with dull pain in the left axilla. Physical signs have persisted throughout. During the exacerbations rales are more numerous and more moist. In the intervals they do not disappear but become distinctly less marked. The patient has kept at hard work regularly and is in excellent physical condition at the present time.

Sputum examinations have been negative for tubercle bacilli on numerous occasions.

July 19, 1916, during an acute exacerbation, cultures showed Streptococcus viridans predominating.

X-ray examination, October 25, 1915, was normal. No abnormal shadows over the left lobe. Slight increase of the hilus shadows. No abnormalities in the parenchyma of the lung.

January 15, 1917, roentgen-ray showed increase of the root shadows with a number of calcareous tubercles at the left root. Pulmonary markings somewhat intensified in both lower lobes, less marked on the left side than on the right.

Case XXI.—E. F., female, aged fifty-three years; first seen November 12, 1915.

Previous History. Double pneumonia at twenty-one when she was very ill, the onset being sudden with a chill and the attack coming on as a complication with measles. Fourteen years later she had grippe with signs in both lower lobes and a diagnosis of pneumonia was made. She was sick five weeks with only a moderate amount of fever. The cough lasted a month longer. Seven years ago she had a recurrence of the cough with expectoration with slight fever for a few days, the cough lasting for six weeks with very little constitutional disturbance. Three years ago she had an attack similar to the last which lasted about three weeks.

Present illness began two months before the patient was first seen with cough and expectoration. She kept at work for a month. She gradually developed a slight temperature, 100° to 101°. She went to bed and the fever subsided in a week. The cough and expectoration continued but gradually improved. A diagnosis of active tuberculosis had been made.

Physical Examination. Over both lobes, particularly on the left side, there was slight dulness and very numerous and very moist rales; no changes in breath sounds. The patient at that time had no fever and was feeling very well.

Course of the Disease. She continued to improve and on November 12, 1915, the signs had almost disappeared on the right side, and were markedly diminished although still present in the left lower lobe. The patient then went South and was next seen June 2, 1916. She had had no coughs or

colds or expectoration and was feeling very well. Examination showed a few rales below the angle of the right scapula and a very slight dulness over the entire lower left lobe.

Sputum examination November 13, 1915, showed pneumococci type IV in almost pure culture.

Roentgen-ray examination June 2, 1916, showed marked increase of vascular markings throughout both lungs, more marked on the right side. At the right base there was irregularity of the diaphragm, apparently due to adhesions.

Case XXII.—Mrs. W. C., aged forty-five years; first seen April 21, 1915.

Previous History. For several years she has been subject to bronchial colds and cough, at varying intervals during which time she occasionally felt a little bit feverish, but had no marked disturbance of general health. During the past winter these symptoms have been particularly marked.

Present History. For the past two weeks the patient has had the grippe with slight fever and marked increase of cough and expectoration. She had been treated for pulmonary tuberculosis and the case was considered as such by me for several months.

Physical Examination. Distinct dulness, diminished breath sounds, numerous moist rales over the entire left lower lobe, few pleuritic sounds over the left axilla.

Course of the Disease. The patient has been under continuous observation since that time. At times she has had practically no symptoms, but the signs in the chest have never changed and at various times there has been a little fever with an increase of cough and expectoration which has sometimes been bloody, and there has been recurrent dull pain in the left side.

Sputum examinations have been persistently negative for tubercle bacilli. Culture, November 9, 1916, showed Streptococcus viridans predominating with few Staphylococci aureus.

X-ray examination, January 14, 1916, showed slight increased density in the left lower lobe. The heart was slightly displaced toward the left.

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DISCUSSION

Dr. Herrick asked whether any of Dr. Miller's patients or any great number of them were Greeks. In the Presbyterian Hospital in Chicago for some years they had had quite a number of patients with pulmonary diseases they knew not how to classify, having regarded them at times as bronchitis, at other times as influenza, again as bronchial pneumonia. Many of them had been of the subacute and chronic character, and so many of these patients were Greeks that they had sometimes spoken of it as the "Greek disease," or "Greekitis."

Dr. Brill said it had been particularly pleasing to him to hear this paper, as it brought out prominently a type of pulmonary disease with which he was familiar for many years and which he had only recently described, though he had been showing instances of the type to his students every year for many years past. In fact, since the great pandemic of influenza in 1890, and whenever an epidemic of influenza recurred in New York City, examples of this type were found. It consists in the presence in the lung of a process which gives rise to an area or areas of fine crepitant rales, with only slight change in breathing and without a great change in percussion. The process was most frequently limited to the left lower lobe of the lung for some reason unknown to him, yet secured more exceptionally in one or both apices. The physical signs of this disturbance may persist for weeks or even months; he has notes of one case in which the evidence of pulmonary involvement lasted four months when suddenly the entire disturbance disappeared. When the apex is involved the constitutional signs are apt to be much more pronounced than when the left lower lobe is involved, in fact being represented by cough, expectoration, moderate fever even of the septic type, and with marked prostration out of all proportion to the amount of pulmonary tissue involved. In fact, the constitutional signs and the physical changes in the lung have led to the diagnosis of pulmonary tuberculosis even by the experts, though in these cases frequent and numerous examinations of the sputum have invariably failed to reveal the presence of the tubercle bacillus, the conclusion being that the cases were examples of pulmonary tuberculosis with negative sputum. One should ever be on his guard lest he fall into this error of diagnosis, though a justifiable one. It is a type of disease which causes more anxiety to the physician than the layman would imagine, because the physician cannot make up his mind whether he is dealing with an instance of pulmonary tuberculosis with negative sputum or whether the patient will not finally be doomed to a more rapid progress of a general tuberculosis. Even the *x*-ray plates of some of these patients show a definite change in

the density of the lung, particularly when one is dealing in the more exceptional cases with apical involvement; then one finds in these plates a diffuse shadow, nothing like the shadow just thrown on the screen in Dr. Miller's first case of lower-lobe process, but more diffuse, less defined, more of the appearance of a haze, without the disseminated punctate appearance of the shadow of the tuberculous involvement of the lung, indicating at least some change in the density of the organ if nothing else. Whether this process was similar to or identical with that of a bronchopneumonia or not the speaker could not say because he had never seen one of these cases at autopsy. He knew, however, that when the constitutional and the physical signs disappeared and the patient was restored to his former health that then the *x*-ray examination of the patient's lung showed it to be restored completely to a normal pulmonary shadow.

Dr. Webb showed slides illustrating chronic cases of different types, and said that in all these cases of chronic non-tuberculous lung infection one should always make a search for streptothrix; and the search for the streptothrix in the same cases should be very prolonged. The streptothrix cases in the lung will be more common than most of us suppose, and, if carefully looked for, will not infrequently be found.

Dr. Hare said it seemed to him that Dr. Miller's paper was of very considerable importance to the entire profession, and particularly to the members of this Association who are often a last resort in making a diagnosis. An error in diagnosis may influence a patient throughout the rest of his life. All of us have recognized the fact that during the last few years the campaign against tuberculosis has caused certain younger members of the profession to think that any variation from the normal or the physical signs in the chest, as impaired resonance, or a slight prolongation of inspiration, or a few rales, or whatever the physical signs may be, are indicative of early tuberculosis, and that the patient should be at once put upon a course of climatic or other treatment designed to oppose the disease in what is called its incipient stage. Two or three years ago the speaker read before the College of Physicians of Philadelphia a paper wherein he attempted to point out what we all know, namely, that there are no physical signs in the early stages of pulmonary tuberculosis which are characteristic, and proceeded thereupon to utter a warning against this tendency to label a large number of people tuberculous. He had done so because a certain number of cases had come to his attention wherein a young man or woman, for example, engaged to be married, had developed certain symptoms by way of impairment of resonance, some prolongation of inspiration, some faint shadow in *x*-ray examination, and the marriage engagement was broken off indefinitely; and in a number of instances young men starting

on a business career gave up everything and went to live in another climate for the rest of their lives because certain physical signs had been found in the chest.

He had been particularly interested in this matter, further, because his colleague, Professor McCrae, had been very much interested in the matter of examining students when they first came to the Jefferson Medical College to determine as to whether they were possibly tuberculous and as to whether they should receive advice as to the continuance of their medical career. His colleague was constantly hearing of young men suffering the bitterest regret that some pulmonary lesion had not been recognized when they first became medical students and that they were not advised to give up medicine, or were not advised to lie by for a year or two and do something else; yet to the speaker it seemed that Dr. Miller's paper and the remarks of Dr. Webb showed how dangerous it was not to recognize the fact that prolonged maintenance of physical signs may exist in the lung without their being in any way due to a tuberculous lesion.

Dr. Solis Cohen said this paper and the discussion made him regret that his great master, DaCosta, never published his clinical lectures or his didactic lectures on the practice of medicine; wherein when the speaker was a student (many years ago) that teacher had called attention, and probably long prior had been calling attention, to this very class of cases. At that time, of course, the tubercle bacillus and the x-ray method of examination were both unknown; but DaCosta had specially called attention to the cases of recurrent bronchopneumonia following influenza. The profession at large in the United States seemed to awaken to the fact that there was such a condition as influenza about the year 1889; but in 1880, when the speaker first listened to DaCosta's lectures, and every year thereafter, he lectured on influenza, because he had been through epidemics. He not only spoke of the epidemics but also of the persistent cause of catarrhal fever as he called it, whereof he said that "like the poor it was ever with us;" but only when it rose to the dignity of an epidemic or pandemic was it commonly recognized. In the speaker's ignorance he had always thought that these chronic bronchopneumonias and recurrent bronchopneumonias following influenza were familiar to the profession at large.

Dr. L. Brown said he had been greatly interested in the paper and voted with pleasure that Dr. Miller's contribution upheld what many tuberculosis workers had long maintained, namely, that when a lesion or physical sign occurred at the base you have to prove that it is tuberculous before you can so accept it. When they occurred at the apex you have to prove that it is not tuberculosis before you can discard such a diagnosis. Dr. Miller had not, he thought, mentioned anything about the condition

of the accessory nasal sinuses in his recurrent subacute and chronic cases; and he should like to ask him the condition of the sinuses in these cases.

Dr. Miller (closing) said the conditions in the cases he had seen were entirely limited to pulmonary manifestations, excepting in some of the influenza cases, that would start in with coryza and occasionally with a slight lobar bronchitis; but there were no infections in any of the *x*-ray sinuses of the upper air passages.

In regard to the nationality, one of these cases occurred in private practice, and no real one class of patients. There were no Greeks among them.

THE PRESENT OUTLOOK OF DIABETIC TREATMENT

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The present diabetic treatment was first applied to human patients three years ago. It is now proper to take stock of what has been learned and accomplished in this time, and of the present therapeutic outlook in comparison with the earlier hopes and prospects.

The most accurate standard of severity of diabetes now appears to be not acuteness of onset, rapidity of progress, intensity of glycosuria, or degree of acidosis. The quick therapeutic relief of these symptoms is sometimes followed by a rather rapid recovery of carbohydrate tolerance, which, however, is limited in every case. In seeking severe cases, the genuinely difficult ones are found to be those in which the tolerance is practically *nil* and shows no appreciable increase even under prolonged rigorous treatment. The question arises why this condition exists, and the answer must be sought in the pathology of diabetes.

The confusion concerning this side of such an important and familiar disease is remarkable. Painstaking studies have failed to clear it up, and it offers problems which are far from solution, but there appears real hope of a solution by following the clues provided by animal experiments. These have shown a specific diabetic degeneration of the islands of Langerhans, characterized by vacuolation of cytoplasm, pyknosis of nuclei, loss of cells and finally almost complete disappearance of islands. Homans showed that the change consists in exhaustion of the special granules demonstrated by Lane and Bensley in the beta cells, probably representing their internal secretion, while the groups of alpha cells frequently

persist with heavy granulation. Martin observed a somewhat different exhaustion also of the alpha cells in some instances. Simple removal of portions of the pancreas does not produce this change if the animals are fed safely within their tolerance, but the process can be set up at any time by overfeeding of the animals predisposed by operation, and the clinical progress of the diabetes and the exhaustion and degeneration in the islands are parallel. The tolerance practically varies with the amount of functional island tissue; and when the islands can still be saved, the animal can be saved, but when the islands are hopelessly exhausted the animal is doomed. This same specific lesion with minor variations has proved typical of the experimental diabetes of a wide range of mammals, from the opossum up to the monkey, and presumably will be found in birds. It was also present in Krumbhaar's dog, the only animal with spontaneous diabetes ever examined for this purpose. It would be strange if human diabetes proved the sole exception to the rule. As a matter of fact, Weichselbaum and Stangl, in advance of any of the experimental results, described what they called hydropic degeneration of the islands in a high percentage of fatal cases of human diabetes. There is no doubt of the identity of the changes described by them with the experimental findings. But the work of these authors has gone almost without confirmation and has not received acceptance by the authorities in either diabetes or pathology. My own study has covered more animal than human material, but two statements seem to be justified at this time. (1) The same specific exhaustion and degeneration of the islands is demonstrable in some human cases as in diabetic animals. These changes are sometimes typically and unmistakably present in pancreatic tissue which has been passed as normal by pathologists of the highest standing. (2) In the few necropsies thus far held upon patients dying at the Rockefeller Institute Hospital the diagnosis of diabetes from the microscopic findings alone is possible in every case. The scarcity of island tissue emphasized by Heiberg and others has been a prominent feature. Exhaustion has been most pronounced in uncontrolled cases dying acutely a few hours or days after admission to the hospital. When the condition has been held completely or partially under control by treatment for a considerable

time, exhaustion may be difficult to find, but the extraordinary fewness and smallness of the islands, the pyknosis of nuclei and scantiness of the cytoplasm, suffice to establish both the diagnosis and the reason for the failure of treatment.

Notwithstanding all descriptions of diabetic lesions in the literature, it remains true that no pathologist is yet able to go through the necropsy material of a hospital and distinguish accurately the diabetic from the non-diabetic cases. Several persons have kindly supplied me with series of unlabelled pancreatic specimens, and it has been instructive to attempt the differentiation. The diagnosis succeeds in some cases, and further information and experience may improve the results. Most physicians and hospitals do not study their diabetic cases adequately on this side. It should be emphasized that freshness of the material is important. Valuable studies can be made upon specimens taken within a few hours after death, but for the best results the interval should be counted in minutes rather than hours. Lack of freshness is doubtless largely responsible for past failures. Separate specimens from three or more different portions of the pancreas are desirable. A good routine fixative is Zenker's, with 1 or 2 instead of 5 per cent. acetic acid, or a neutral formaldehyde-bichromate-sublimate fluid. The granule stains are especially beautiful and promising, but the ordinary eosin with hematoxylin or methylene blue is useful. In regard to the belief that the animal experiments and the therapeutic innovations together open up some new view-points which justify a revival of interest in the pathological investigation, the following suggestions may be made.

1. The customary plan in the past has been to compare series of diabetic and non-diabetic specimens, with the result that pancreatitis, cancer, arteriosclerosis, hyaline deposit, and structural abnormalities of the islands have been found in both classes, though, as a rule, more markedly among the diabetics. Opie, of course, did not claim that hyaline degeneration is the specific lesion of diabetes. He merely used the observation of certain cases in which the islands had thus degenerated, while the acinar tissue was largely normal, as a basis for the insular theory of diabetes, which has since been thoroughly established. It should be pointed out that comparisons

of the above type cannot found a pathological diagnosis. If these or any other processes destroy islands of Langerhans, a diabetic tendency is created to just that extent. It is necessarily difficult for a pathologist to decide just when the destruction is sufficient to bring on diabetes, or whether weakness or other disturbances prevent the symptoms from becoming manifest. When the sugar tolerance of the supposedly non-diabetic cases has not been tested, and especially in cases of pancreatic disease, it is obviously impossible to draw any absolute line between the diabetic and non-diabetic condition.

2. The traditional mystery has been that patients should die acutely with the supposedly severest type of diabetes, and the pancreas be found free from inflammatory or other evident changes and containing a fair abundance of islands of Langerhans. The numerous reports of this character have served as the principal argument against the island theory. But it is now known that such cases are capable of quick transformation. For example, though the diabetes in Geyelin and Du Bois's patient was perhaps of the greatest intensity ever demonstrated by accurate methods, there was a rapid recovery of tolerance running into hundreds of grams of carbohydrate. Formerly, if this patient had died in coma after only a month or so of diabetes, it would have been puzzling to find a normal-looking pancreas with numerous islands, but it is now plain that the islands must be there or the sudden improvement would be impossible; and the island theory instead of being irreconcilable with such facts would be untenable if they were otherwise. Such patients have not died in the past because of any severity of their diabetes, but they have died in a relatively mild stage of their diabetes because of improper feeding, particularly from coma due to fat. Such early deaths may still be excusable if the patient is in coma when first seen, or if disobedient, or if there is a complicating infection or other accident. Otherwise, tentatively at least, the opinion may be ventured that if a diagnosis of diabetes is not possible at necropsy from the simple quantitative deficiency of island tissue, the fault lies with the clinician rather than with the pathologist. This is a provisional statement which invites attack. Perhaps it is too extreme. But we shall be willing to let

others explain their diabetic deaths without organic pancreatic changes, if we can continue to explain our deaths by organic pancreatic changes. For the present my belief is that the true severity of diabetes depends upon the amount of functional island tissue present. I hope we shall never have a treated patient die with a quantity of island tissue which would cause any pathologist to be in doubt concerning the diagnosis; and, if it proves valid, this opens an interesting possibility for those who either hold or deny that treatment has improved, to examine the pancreatic specimens preserved from years back, and to decide whether death now occurs with milder or more severe diabetes as judged by pathological evidence.

3. The diagnostic significance of exhaustion and degeneration of island cells requires fuller discussion. If this is a specific diabetic process it might be deemed sufficient to look for it as an infallible test. The conditions are not so simple, but, on the contrary, involve important questions concerning which little is known. Study must be devoted to the interpretation of the absence or presence of this change.

(*a*) *Its Absence.* The failure to find visible exhaustion and degeneration apparently does not exclude the existence of severe and active diabetes, and this seems to be also the conclusion of Homans. A hypothetical explanation is suggested by the animal experiments, where the exhaustion is invariably and prominently present. For one thing the state of extreme vacuolation is probably a terminal one for any island cell. It probably dies and disappears soon afterward. The cells perhaps differ slightly in resistance in different species. Such higher resistance may perhaps explain the unusually striking histological pictures presented by the cat. If it should prove that the terminal stage of the human cell is brief and its membrane ruptures easily, the process would be less frequently seen and harder to recognize. More definite and important is the fact that the course of experimental diabetes is rapid, and within a few days or weeks the islands are destroyed to such an extent that no length of fasting can check the diabetes. Such a thing seldom occurs in human cases. Almost every patient can become sugar-free if able to endure prolonged fasting. Whether because the entire

pancreas is present instead of a small fraction, or for some other reason, the break-down of the human islands often requires many months or years, and is further slowed by treatment. It is therefore not surprising if the terminal decay of the cells is often missed microscopically.

(*b*) *Its Presence.* Probably the specific exhaustion is actually visible if properly looked for in a considerable proportion of the most active cases uncontrolled by treatment, where the destruction of islands is most rapid. The discovery of so many such instances by Weichselbaum and Stangl is more complimentary to their power of microsopic observation than to the clinical care of the patients. In animals this lesion is specific and diagnostic. A single cell definitely and unmistakably exhausted gives the diagnosis of diabetes or a diabetic tendency. The question is open whether the meaning is equally positive in human tissues. My own study is not far advanced, but I have not seen a normal pancreas, or a pancreas after death from infectious disease, which showed anything resembling this exhaustion. The doubts and difficulties have thus far been in connection with metabolic and pancreatic diseases. In other lines the pathologist corrects the clinician, not *vice versa*. The same will hold true if any pathological diagnosis is ever established for diabetes, and it has perhaps been too readily assumed that clinical diagnosis is infallible for diabetes. It should be borne in mind that diabetes is something deeper than glycosuria or hyperglycemia. These have sometimes been reported transitory or absent in animals nearly or totally depancreatized, especially if there is serious undernutrition or injury. The absence of active diabetes with extensive destruction of the pancreas by tumors is probably largely a matter of digestive disturbance and emaciation. As will be mentioned shortly, some degree of exhaustion can occur in dogs when there is only a tendency to diabetes. In one human pancreas I found an appearance of exhaustion in a few island cells, when the clinical diagnosis was chronic nephritis with hypertension and uremia. In view of the frequency of hyperglycemia with this form of nephritis, also the occasional lipemia, as well as a few reports of suppression of diabetes by nephritis, such a finding is not necessarily a contradiction of the specificity of this picture.

4. There is the question of the immediate cause of the changes. Homans regards the exhaustion and degeneration as the result, not the cause, of the diabetes. One important fact is that animals depancreatized to just the right degree may come to show a sugar tolerance almost as high as normal, yet some degree of exhaustion is found in their islands. Maximal sugar feeding of such animals may finally bring on diabetes, or the attempt may fail permanently, but diabetes then may be possible by removal of only a fraction of a gram of additional pancreatic tissue. Without attempting too fine distinctions in the definition of diabetes which might here be involved, it may be accepted as probable that the exhaustion is what the word implies, namely, a discharge of the internal secretory granules from the cell more rapidly than they are formed. This is an important and perhaps unique physiological demonstration of overstrain and consequent death of internal secretory cells under a functional stimulus. It is not known whether any other stimulus than food can produce this exhaustion, or by what mechanism food acts to produce it. The natural paths of nervous supply to the pancreas are not essential to the process, for typical exhaustion has been obtained in subcutaneous grafts with all intra-abdominal communications cut. It is probable that the ganglia within the pancreas can also be excluded by experiments mentioned below. There is clinical importance in the fact that anatomical degeneration of island cells is produced by feeding beyond the tolerance, or even to a degree that places a strain upon the tolerance, and also in the possibility that this may be the only cause that produces this form of island destruction. The extreme scarcity of island tissue at necropsy serves as justification for the therapeutic management in one way, but not in another. It absolves from the responsibility of having let a patient die from some acute accident at an early stage of diabetes, but it does not prove whether the treatment conserved the tolerance as long and perfectly as possible. The worst form of treatment is that which permits early death from coma or similar avoidable accident, as has been so common in the past. The next worst is the treatment which continually keeps the tolerance more or less overtaxed with fat or any other food and perhaps relies upon occasional fasting or undernutrition to ward off acute

dangers, while all the time destroying islands which can never be replaced, until finally the patient either dies with demonstrable dearth of island tissue, or by a change of treatment is barely kept alive without hope of regaining any appreciable assimilative function.

5. There is the further question of the remote cause of these changes, which involves the cause of diabetes itself. Aside from gross and obvious pancreatic destruction, what is it that originally reduces a patient's pancreatic function to a point where he, like a partially depancreatized dog, becomes susceptible to this form of injury from food? The hypothesis of infection has recently attracted notice, and has received support from the occasional occurrence of permanent or transitory diabetes following acute infections. An infectious inflammation of the pancreas itself is one conceivable cause of such diabetes. The production of diabetes by pancreatic inflammation has been demonstrated experimentally. Such inflammation has been produced by pressing between the fingers and in other cases by cutting off the circulation by means of rubber-covered clamps for some twenty to eighty minutes. By this means dogs have been made diabetic with as much as a fourth or a third of the pancreas present.[1] The study is not complete, but the immediate result seems to be a hardened but not fibrous pancreas, with widespread degeneration and regeneration. The islands suffer more than the acini, because of either lower resistance or less regenerative power. It is to be investigated whether the pancreatic ganglia are destroyed. With proper technic the end-result is not fibrosis, but rather a soft, normal-appearing pancreas, distinguished from the normal chiefly by its deficiency in island tissue. The noteworthy features are a pancreatic inflammation with scarcely perceptible impairment of digestion or other clinical symptoms, and the clearing up of this inflammation, leaving a pancreas of the type often found in diabetes. It is possible to think of pancreatic inflammations set up by infection, by bile, or other injuries. It is also noteworthy that surgeons operating on the biliary tract often report hardness in the pancreas. Perhaps later at necropsy the pancreas is of normal consistency. It now appears that the surgeon is not necessarily in error, and that such

[1] The successful cases are important for study, but the method is difficult, uncertain, and not a convenient routine method for obtaining diabetes.

pancreatic induration may be important in setting up either diabetes or a tendency to it. The diabetes caused by pancreatic inflammation in dogs may be mild or severe, transitory or permanent. It possibly corresponds to some proportion of human cases.

On the other hand, such experiments tend to rule out the hypothesis of pancreatic infection or inflammation as the cause of other clinical cases, including some of the severest ones. The reason lies in the numerous observations above mentioned, of patients dying early after the most intense diabetes with an abundance of fairly normal-appearing islands. Pancreatic inflammation leads to no such picture.

In a series of miscellaneous pancreatic specimens furnished me by Drs. Lambert and Evans, of the Presbyterian Hospital, there was a particularly interesting one showing a fully normal quantity and arrangement of island tissue, but with unmistakable exhaustion in rare individual cells. This was surprising in tissue which I had supposed non-diabetic, but reference to the case description showed that death followed operation for carbuncle and the urine contained sugar. It is still necessary to assume some marked functional impairment not merely of the few exhausted cells, but particularly of the great mass of those which appeared microscopically normal. It is especially surprising that such extreme functional disorder must be supposed at this early stage, and yet later the question of successful treatment seems to come down practically to the anatomical mass of functional island tissue present. With regard to the functional capacity, notice may be necessary of the above-mentioned scanty cytoplasm, pyknotic nuclei and other occasional appearances other than exhaustion. Some persons accept the possibility of a toxic origin of this disturbance from distant foci of infection, but this is pure speculation at present. It is true that diabetic patients are injured by intercurrent infections and should be relieved of any known foci of infection, but the same is true of any form of injury, including nerve-strain. The theory of hereditary and nervous disturbances is the classical one. In one instance already reported I definitely produced permanent diabetes by the Bernard puncture in a partially depancreatized dog which was not diabetic before the puncture. This country is now undertaking participa-

tion in the most extensive test of this theory ever known. The shell shock and injuries of the nervous system inflicted in this war, along with the psychic strain, must either produce a host of diabetic cases or bring the collapse of the nervous hypothesis. Some case reports from Europe describe the onset of diabetes in young soldiers on service, but of course the same happens to some individuals at home in peace times. There is a report that glycosuria has not been frequent among the victims of traumatic neurosis and related injuries, but I have not yet had replies from men to whom I addressed inquiries on the point. If there is such a thing as traumatic diabetes, as has seemed probable in the past, the old rule may be called to mind, that the prognosis, even for full recovery, may be good if the condition is checked early, but is bad if the diabetes is allowed to continue several months. On the practical side, radical and thorough treatment is indicated. On the scientific side, there will be interest not only in the clinical histories but also in any pancreatic specimens obtained.

Briefly, then, diabetes mellitus is a weakness of assimilation of food, due to deficiency of the internal secretion of the islands of Langerhans. The treatment thus far is purely functional, and is successful in proportion to the efficiency with which the weakened function is spared. There is a question, even if we succeed in preventing the cell degeneration due to overfeeding, whether the original cause behind the diabetes continues to act so as to make continued downward progress. A class of patients must be recognized whose island capacity is so low that even the lowest metabolism compatible with life slightly overtaxes it, so that degeneration of cells continues slowly in spite of the most radical treatment, and death is only delayed and not prevented. The improvement in less extreme cases, barring infections and indiscretions, seems opposed to the belief in inevitable downward progress. Our records for three years comprise 30 cases admitted during the first year, and a total of 90 cases. Two-thirds of the total number are alive and three-fifths of those admitted in the first year are alive. Some deaths were acute ones before there was a chance for treatment, some were due to faults of the patients, some were due to mistakes in the treatment, and some were due to failure of the treatment to control

certain cases, even under the best conditions. This is by no means the best record possible. It could be improved if the thing could be done over with the advantage of present experience. But it is not a bad record in view of the type of cases treated. No diabetic treatment can be a cure, but yet pessimists ought not to treat diabetes. The present method is not merely a time-saving device or a temporary safeguard against coma or other acute dangers. It represents a new principle in sparing the tolerance for all classes of foods, including fat. The results are believed to be not only a greater prolongation of life, but at the same time greater comfort and usefulness than was the lot of diabetic patients before, especially through avoidance of the traditional complications. The islands of Langerhans constitute a vital organ, and denial should be made of any supposition that benefit results from breaking them down in function or structure. The indications are that the present treatment spares them as efficiently as possible by a dietetic method, and that essential further progress is now to be sought not along the line of functional sparing, but rather in some remedy potent enough to make good an organic defect. Some have looked for such an aid outside the pancreas, in an imaginary balance between endocrine glands. It is believed that existing experimental evidence overthrows such hopes. The danger of confusing the symptoms with the fundamental disorder has already been warned against. A new example is offered by the fact that in a diabetic animal under suitable conditions thyroidectomy may produce a remarkable improvement from the stand-point of hyperglycemia, acidosis, and apparent food tolerance, but necessarily the specific and vital function of the islands of Langerhans is not restored, and the animal goes on into fatal cachexia, injured and not benefited. A cure of diabetes can consist only in supplying artificially the internal secretion of the islands, or in actively building them up anatomically as well as functionally. It may be conceded that we are dealing not only with an anatomical deficiency of islands, but, in addition, with exhaustion of a possible normal power of regenerating island tissue. Nevertheless, physicians and patients should persevere to the uttermost in the treatment by functional rest, not only as the means for the greatest present welfare, but also in the hope of more positive and powerful therapy to come.

DIABETES IN CHILDREN

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AND

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Among the private cases of diabetes coming under the observation of the writers, 4.7 per cent. fall in the first decade of life. Von Noorden records 1.4 per cent. of his cases in this epoch, and his statistics exceed those of Frerichs, Seegen, Grube, Schmitz, Pavy and Külz by nearly a half. In our opinion these statistics denote an increased frequency of recognition of diabetes in children rather than any increased frequency of the disease.

The same etiological factors are found in children as in adults, but obesity, dietary excesses, heredity, mental overexertion are those most commonly observed. As an instance of the last, at one time four children were under our observation who were at the head of their respective classes at school. Not rarely is the diabetic child the only child in the family.

Kisch directed attention to the frequency of the development of diabetes in the later lives of fat children, and we never see a fat child without thinking of this possibility, for a fat child, like a fat man, is prone to diabetes. Particularly serious must it be for a child or adult of slight stature to put on weight which would be excessive even for a man of large frame. Case No. 1142 first consulted me at the age of forty-one years, and I can just remember his little spindling legs and delicate frame as a boy before he entered the primary school; many years later he entered a grocery store, "worked like the dickens and ate the same way," until, at the age of forty, he was sixty pounds above the average weight, and sugar was found at a life insurance examination.

One of the most striking instances of the effect of obesity, combined with infections, is that of a little child, Case No. 1139, a healthy baby until his second year, when he entered upon a series of rhinopharyngeal and bronchial attacks, including a mild bronchopneumonia. During eleven of these feverish illnesses exercise was curtailed, and he was kept abed to safeguard his heart. A cow was bought that he might have fresh, rich milk, and to the 50 ounces of this milk which he daily consumed were added 3 tablespoonfuls of a malt preparation, amounting in nutritive value to 120 or more calories. At the end of his first year he was of normal weight, but at eighteen months his weight was above that of a child of two years. When two years old his weight had increased to that of a child of three years and a half, and when two years and a half old his weight was above that of a child of four years. Is it surprising that when mumps developed glycosuria appeared? It vanished with a change in diet, to return three months later, during the presence of another mild febrile disorder, and again in six months after the removal of adenoids, but since the urine has remained sugar-free. Encouragement is derived from the presence of these etiological factors, for to a considerable extent they are susceptible to prophylactic treatment.

The improvement in the treatment of diabetes in children is shown by our statistics. Thus the number of fatal cases with a duration over five years has been 2, but the number of living cases with a duration in excess of five years, at the compilation of these data December 1, 1916, is 4. Excluding these 6 cases of unusual duration, there were, for the period 1901 to December 1, 1914, 30 fatal cases with an average duration of one and one-tenth years, and for the period December 1, 1914, to December 1, 1916, 15 living cases, with an average duration of one and six-tenths years—a gain of nearly 50 per cent. It is true that this represents a short period of life preserved, and often not a particularly happy one, but the point is that the general treatment of all cases has improved and the exceptional case now stands a chance for marked improvement.

A child with an hereditary history of diabetes has a more favorable outlook, according to our experience, than the child whose family is free from the diabetic taint. This is shown by the following

table, though only 1 of the 3 cases fall in the first decade; the favorable cases of Riesman,[1] Teschemacher's[2] cases of apparently cured diabetes, and the case of Schmitz, quoted by Naunyn,[3] all were hereditary. In fact, Naunyn's own famous cases—not by any means all children—were hereditary cases. This circumstance leads us to reassure to some extent adult patients with diabetes, but at the same time to point out the advisability of prophylaxis along the lines indicated above.

THE FAVORABLE INFLUENCE OF HEREDITY UPON THE COURSE OF DIABETES

Case No.	Age at onset.	Hereditary history.	Outcome.	Duration.	
				Years.	Months.
203 . . .	7	Mother	Alive	10	1
295 . . .	14	Father, also brother	Coma	12	
304 . . .	13	Grandfather, also two brothers	Coma	9	2

A blood-sugar below 0.09 per cent. has been found in 6 children. To the unwary this might be considered as evidence against actual diabetes and for renal diabetes. On this point we would say "Beware!" Repeatedly we have seen children with low blood-sugars subsequently develop progressive diabetes. The prognosis is so serious for the diabetic child that each case should be strenuously treated.

Complete disappearance of diabetes is apparently possible in children. Schmitz's case, above cited, is one of the best, and Case No. 203 of our series is most encouraging. This little boy first showed sugar at the age of seven, April 5, 1908, although symptoms were present the preceding year. His mother has diabetes and is Case No. 155. He was promptly put upon a careful diet by his mother and physician, Dr. Warren White, of Roxbury, Mass., and has remained sugar-free during the subsequent nine years.

He was very faithful to his diet and remains in good condition. By advice he is purposely keeping a trifle under weight and eats a

[1] Am. Jour. Med. Sc., 1916, cli, 40.
[2] Deutsch. med. Wchnschr., 1910, xxxvi, 401.
[3] Der Diabetes Melitus, Wien, 1906, p. 384.

normal diet except for a little less sugar. The faithfulness of his mother to her diet maketh a doctor's heart glad! Though she has had diabetes sixteen years, she "would not touch sugar any more than she would poison!"

Von Noorden reports a striking case of a seven-year-old boy, who, on a strict diet, constantly excreted 20 to 30 grams of sugar and considerable quantities of acetone bodies. He became sugar-free only with the help of oatmeal and vegetable days. He remained on this restricted diet for some years, and at the age of twelve years was again seen by von Noorden, when he was in perfect health, eating an ordinary diet without a trace of glycosuria.

When death has occurred in a diabetic child it has been due in all but 1 of our cases to coma, but in the exceptional case it took place with inanition and anasarca. A little boy, Case No. 1120, aged seven years, with diabetes of nine months' duration, beginning with 7 per cent. of sugar, entered the New England Deaconess Hospital in September, 1916. He had been thoughtfully treated in Vermont, but the urine had not remained sugar-free for more than two weeks at a time. One week before entrance his case became serious; nausea and deep respiration existed, and a strongly positive ferric-chloric reaction appeared in the urine. He became drowsy and dull, but not entirely unconscious, two days before entrance. He was fasted for the three days before entrance and given 1 teaspoonful of sodium bicarbonate three times a day. Upon arrival at the hospital his condition had improved, but the carbon dioxide in the alveolar air was 21 mm. mercury, and it fell to 18 mm. the following morning. There was a slight trace of albumin in the urine and a few finely granular casts. With fasting, the omission of alkalis and small quantities of carbohydrate and protein he became sugar- and acid-free, and later tolerated carbohydrate 3 grams, protein 20 grams and fat 24 grams. Efforts to increase the diet without the return of sugar or acid failed; acidosis and anasarca appeared.

October 23. The protein and fat of the diet were increased, and acidosis became extreme, deep breathing ensued, and the carbon dioxide in the alveolar air fell to 15 mm. mercury on repeated occasions; but again with fasting and without alkalis the acidosis

disappeared. From this time on he gradually failed, anasarca increased and at length petechiæ developed and he died without coma from exhaustion.

Slowly but steadily coma as a cause of death in diabetes is decreasing. The fact that it has been so frequent in children should awaken a hopeful rather than a discouraging outlook. As a rule coma is avoidable during the first and second years of the diabetes, and to a large extent later if favorable treatment along modern lines is followed.

Children make exceptionally good patients. This is probably due to an early discovery of the disease and to vigorous treatment. Almost invariably children become sugar-free for a shorter or longer period. The diet is borne unusually well, and, as a rule, without complaint. In favorable cases growth takes place quite as in healthy children, and it is this growth which often deceives the physician and relatives into believing that the disease has disappeared and has led to relaxation in treatment. In other cases growth is retarded. In such instances it is encouraging to remember that Osborne and Mendel[1] state, as a result of their experiments upon animals, that "after periods of suppression of growth even without loss of body weight, growth may proceed at an exaggerated rate for a considerable period. This is regarded as something apart from the rapid gains of weight in the repair or recuperation of tissue actually lost. Despite failure to grow for some time the average normal size may thus be regained before the usual period of growth is ended."

The methods of treatment of children with diabetes are precisely those of adults. Rigid dieting offers more comfort to the child than to allow freedom in eating, and, furthermore, I am convinced that rigid dieting is more effective in prolonging life than neglect to follow dietetic rules. Parents occasionally renounce regulation treatment and adopt quack methods. In not a single instance has the child done as well as before the change was made, and my statistics pay the penalty.

The diet of children with diabetes from the age of two years upward requires surprisingly few modifications from that of an adult.

[1] Am. Jour. Physiol., 1916, xl, 16.

Fasting is borne perfectly well for a few days, and with comparatively little complaint. Even the complication of a slight temperature and a croupy cough (not diphtheria) does not interfere with the fasting treatment. Following the period of fasting the addition of 50 grams of 5 per cent. vegetables with broths goes a long way toward relieving hunger, and subsequent weekly strict diet days cause no trouble if broths and 300 grams of 5 per cent. vegetables can be allowed. Special pains should be taken in the preparation of the vegetables, for children eat fast and occasionally diarrhea results. Strange to say, more frequently the complaint is of constipation. Children's specialists, accustomed to dealing with children of delicate digestions, sometimes err in making the diet too simple. In our experience with diabetic children of two or three years of age and over, they easily bear the diet of adults if reasonable care is taken.

ACETONE BODIES IN THE BLOOD IN DIABETES

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THERE are two prevalent views as to the cause of death in diabetic coma. One attributes it to acidosis from which the patient dies in the same way that Walter's animals died when given excessive doses of mineral acids; the other assumes that a specific intoxication occurs where acidosis, if present, is but casual. Both views have arguments in their favor and are based upon the fact that diabetic coma is accompanied by an increased production of the three acetone bodies. To determine which of these opinions is correct, it would be necessary to compare in fatal cases, blood and tissue analyses for acetone bodies, with observations upon changes in the blood alkalinity made during life. Heretofore this has not been done because there were no sufficiently accurate methods.

Recently it has become possible to estimate the degree of actual acidosis in several ways and to determine quantitatively the total acetone body content of both blood and tissues. Sassa and Mariott have demonstrated that the blood and tissue acetone is abnormally high in conditions of diabetic acidosis, and that when the tissue acetone is increased so is that of the blood. This paper summarizes further studies in diabetes upon the acetone bodies in blood and urine and their relation to acidosis. No tissue analyses were made because autopsy material was not available.

The methods used were devised by Van Slyke. The degree of acidosis was measured by the combining power of plasma for CO_2. The total acetone bodies, including acetone, diacetic acid, and beta-hydroxybutyric acid, were determined and expressed as acetone by his gravimetric method.

At the outset it was found, in confirmation of previous work, that normally there are but traces of total acetone in blood and urine. Pathologically the blood acetone may rise to a concentration of over 300 mgm. per 100 c.c., and the excretion of acetone in urine may equal over 9 gm. per liter. Of the blood acetone about half or two-thirds occurs as beta-hydroxybutric acid, the rest as diacetic acid, with relatively small amounts of free acetone. Most of the total acetone occurs in the plasma. Under certain conditions, however, the corpuscles may take up these bodies so that corpuscular acetone may be greater than that of plasma. In the urine about two-thirds of the total acetone is derived from beta-hydroxybutyric acid and the rest from acetone and diacetic acid. As excretion increases, relatively a larger proportion is represented by beta-hydroxybutyric acid. There is no essential relationship between the different fractions in blood and urine.

Since plasma was used to measure the degree of acidosis, and since it contains more acetone than whole blood or corpuscles, its total acetone content was used for the work reported. It seemed of greatest interest to compare the accumulation of total acetone in the blood with the degree of acidosis as measured by the plasma-combining power for CO_2. A series of 100 cases was tabulated in which simultaneous observations were made upon these two factors. Some of the cases had severe acidosis, others were acid-free and had been eating a carbohydrate-rich diet for considerable periods. No comatose cases were considered and none had received alkali. The result of such a comparative study showed there was no quantitative relationship between increased concentration of total acetone bodies in the blood and lowering of the blood bicarbonate. In a general way the blood acetone rose as the bicarbonate diminished; beyond this no conclusion could be drawn.

An attempt was made to compare the excretion of acetone bodies in the urine with their concentration in the blood. This was done in two ways. Total blood acetone determinations were made each morning before breakfast. Urinary total acetone determinations were made upon twenty-four-hour specimens for the same day. Excretion of acetone diminished more rapidly than did its accumulation in the blood, although the two tended to parallel one another.

It seemed possible that a closer relationship between excretion and accumulation might be shown by using some form of constant as devised by Ambard for urea and chloride. Short period tests were used when the urine was collected for a given interval of time, and blood was withdrawn at about the middle of the period. Results in this way were more suggestive, but at present inconclusive.

The total acetone bodies were affected by several procedures. Large amounts of fat increased the total acetone in both blood and urine. The maximum increase occurred several hours after ingestion and a few hours after the visible alimentary lipemia disappeared. Small amounts of fat, even in the absence of carbohydrate, diminished the total blood acetone. Fasting or a pure carbohydrate diet diminished a high blood acetone, although it was possible for a slight acetonemia and acetonuria to persist even after a patient had been receiving increasing amounts of pure carbohydrate for a week or ten days. Sodium bicarbonate caused a marked increase in output of total acetone. The effect of this drug on the blood acetone is less certain. A few cases were studied to determine this, but the evidence is not clear and no conclusions are justified.

Three fatal cases of coma were studied. In one case the combining power for CO_2 in the plasma was 14 volumes per cent. and the total plasma acetone was 54.5 mgm. per 100 c.c. The patient was given 25 gm. of sodium bicarbonate by mouth. Death occurred a few hours later. Blood removed shortly before death had a combining power for CO_2 in the plasma of 17 volumes per cent., and the total plasma acetone was now 97.8 mgm. per 100 c.c. Three observations were made in a second case which did not receive alkali. The first plasma bicarbonate reading was 18.9 volumes per cent. with a total plasma acetone of 71.2 mgm. per 100 c.c. Twenty-four hours later the plasma bicarbonate reading was 17.1 volumes per cent. and the total plasma acetone 107.2 mgm. per 100 c.c. The third reading at the time of death twelve hours later was 26.7 volumes per cent. for the plasma bicarbonate and 127 mgm. of total acetone per 100 c.c. of plasma. The third case was practically comatose for eight days. For six days the patient fasted and received alkali. The combining power for CO_2 in plasma rose from 22.1 volumes per cent. to 50.2. The total plasma acetone rose from 83.8 mgm. per

100 c.c. at entry to 368 mgm. The patient was fed on the last two days of life and received no more alkali. The plasma bicarbonate on the day before death was 48.5 volumes per cent. and the total plasma acetone 192.5 mgm. per 100 c.c. All three cases therefore had a marked increase in the plasma acetone occurring before death. Two cases received bicarbonate, the one not receiving it, however, had as rapid a premortal rise in blood acetone as the comparable case which was given it. Two cases, possibly, died of acidosis. One case died without acidosis but had the most striking increase in the total plasma acetone of the series. The significance of these findings is not explained.

In conclusion the two important points brought out by these studies are:

1. There is no quantitative relationship between the degree of acidosis in diabetes as estimated by the combining power of plasma for CO_2 and the actual concentration of total acetone bodies in the blood plasma.

2. Diabetic coma in the three cases studied was accompanied by a rapid premortal rise in the total plasma acetone bodies. In one case this was independent of acidosis.

THE MAINTENANCE DIET IN DIABETES MELLITUS AS DETERMINED BY THE NITROGEN EQUILIBRIUM

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In the treatment of diabetes mellitus there are two guiding principles which determine the caloric value of the diet. In the first place, the quantity of carbohydrates, proteins and fats offered the patient must be within his carbohydrate tolerance; that is, the diet must be so regulated that the urine remains sugar-free. It is generally acknowledged that under these circumstances the disease itself is treated in the most effective manner. Secondly, a diet of sufficient caloric value should be offered the patient, so that his health and strength may be maintained at a normal level. It is readily appreciated that these two guiding principles of treatment are diametrically opposed to one another in many respects. The one demands a restricted diet and in many instances under-nutrition; the other calls for a larger amount of food. The first aims at treating the disease, diabetes mellitus; the second attempts to conserve the nutrition of the patient. The neglect of either factor may entail undesirable results.

During the past years emphasis has been continually placed upon the dietary restriction and the prevention of glycosuria. Previously, on account of lack of full appreciation of the results which could be obtained by a more drastic curtailment of the food calories, this idea was not pushed to its logical conclusion of controlling the glycosuria of nearly every diabetic patient. Through the efforts of F. M. Allen, by systematic and radical reductions in the food, this may be easily accomplished in most cases.[1] The widespread use of these

[1] Allen, F. M.: Boston Med. and Surg. Jour., 1915, clxxii, 241.

very limited diets has brought up the question of how little the individual may eat and yet remain physically and mentally fit. It is the object of the present paper to furnish at least a partial answer to this problem.

At present it is believed that "diabetics generally have no higher food requirement than normal, and on account of undernutrition and lessened muscular activity will tend to maintain equilibrium on a smaller number of utilizable calories than normal persons."[1] One factor which the above statement implies is that the lower the nutritional state of a diabetic or anyone else becomes, the less will be the food requirements necessary to reach a maintenance level. When such a subnormal state is reached, and the main object of treatment is to keep the patient alive and not necessarily efficient, a partial failure in our therapeutic aims must be acknowledged. The maintenance diet, under ideal conditions, should be sufficiently high, not only to enable the patient to live, but also to carry on an average amount of physical and mental work without undue fatigue.

The standard for maintenance for the diabetic may be sought in one of two criteria, (1) the caloric requirement, and (2) the nitrogen equilibrium. The caloric requirement may be readily ascertained according to the height-weight formula of Du Bois and Du Bois.[2] Food administered in accordance with this standard[3] should satisfy all theoretic demands. The nitrogen equilibrium represents the lowest possible diet which could be exacted of any patient. Food, under these circumstances, results in the conservation of the protein tissues, but does not necessarily prevent the loss of fat. This principle has been applied in the treatment of obesity; it was successfully used in the prolonged dietetic experiments of Chittenden on normal people, and is employed here. No living being can afford to lose muscle and glandular tissue indefinitely. How far the fat store of any individual may be depleted with advantage is another question. There is much to be said in favor of allowing the diabetic to become thin, so that his metabolism may be established at a lower level, as has so frequently been urged, but it should be distinctly appreciated that this loss of weight should

[1] Allen, F. M., and Du Bois, E. F.: Arch. Int. Med., 1916, xvii, 1010.
[2] Du Bois, D., and Du Bois, E. F.: Arch. Int. Med., 1916, xvii, 863.
[3] Gephart, F. C., and Du Bois, E. F.: Arch. Int. Med., 1916, xvii, 902.

occur in the fats and not in the vitally necessary proteins. It is with these ideas in mind that the nitrogen equilibrium has been chosen as the lowest possible food standard by which diabetics may be maintained in a state of physical and mental well-being over longer periods.

TABLE I.—Diets of Specified Caloric Value in which the Fat is kept at a Low Level. The Protein and Fat are Approximately Equal to Each Other, Gram for Gram. From these Tabulations, Approximate Diets of any Caloric Value may be Readily Calculated. These are the Diets Used in Most of the Present Observations.[1]

Food.	500 calories, Gm. or c.c.	1000 calories, Gm. or c.c.	1500 calories, Gm. or c.c.	2000 calories, Gm. or c.c.
BREAKFAST—				
Eggs	(1) 50	(2) 100	(2) 100	(2) 100
Bacon[2]	40	50	60	
Ham				75
Butter	..	5	10	15
Vegetables[4]	..	..	..	100
Black coffee				
DINNER—				
Broth	150	150	150	160
Steak[3]	40	100	140	160
Vegetables[4]	200	200	200	300
Cream cheese	..	..	20	30
Butter	5	10	15	20
Olive oil	..	10	15	15
Black coffee				
SUPPER—				
Broth	150	150	150	160
Eggs	..	..	(1) 50	(2) 100
Steak[3]	40	75	100	140
Vegetables[4]	200	200	200	300
Butter	5	10	15	20
Tea (plain)				
TOTAL VALUE OF—				
Protein	40.4	71.2	99.9	135.7
Fat	31.0	71.6	110.7	144.4
Carbohydrate	12.0	12.0	12.5	21.7
Calories	503	1006	1489	1986

The kind of food provided for the diabetic may ultimately prove to be of more importance than is accredited to it at present. That a protein-fat diet low in carbohydrate should be employed is common

[1] For complete details of these diets, see Jour. Med. Soc., New Jersey, 1916, xiii, 339.

[2] The bacon is weighed uncooked. The fat and protein content is calculated for the cooked product.

[3] The caloric equivalent of other carbohydrate-free meat or fish should be frequently substituted from the accompanying list (Table II), to furnish variety in the diet.

[4] Two or three different vegetables should be chosen from the accompanying list (Table II), which tabulates the vegetables containing 5 per cent. or less of carbohydrates.

knowledge. However, the proportion of fat and protein, and the height to which the protein-fat foods are raised before carbohydrates are added are still open questions which are answered in widely divergent ways by different clinicians. In the present observations the diets outlined in Tables I and II were used whenever possible. These are as low in fats as it is possible to make them and yet render them palatable over long periods and they afford the maximum variety of which a carbohydrate-free diet is capable. The low fat content of these diets was insisted on as being the most satisfactory manner in which to control acidosis. It may be noted that the fats and proteins remain approximately equal to each other, gram for gram, throughout these diets.

TABLE II.—List of Meats, Fish and Vegetables Allowed in the Diets of Table I. The Meats are Tabulated in Units Approximating the Caloric Equivalent of Ten Grams of Beefsteak, and may be Substituted for the Same Caloric Value of Beefsteak in Table I.

CALORIC EQUIVALENT OF 10 GMS. OF STEAK IN CARBOHYDRATE-FREE MEAT OR FISH

Food.	Gm.	Fat, Gm.	Protein, Gm.	Calories.
Steak	10	1.0	2.4	19
Roast beef	5	1.4	1.1	18
Tongue	7	1.4	1.6	20
Lamb chop	5	1.5	1.1	18
Roast lamb	8	1.3	1.6	20
Sweetbreads	11	0.1	4.4	19
Boiled ham	7	1.4	1.5	19
Fried ham	5	1.7	1.1	20
Roast pork	9	0.9	2.6	19
Bacon	9	1.7	0.9	20
Chicken	11	1.0	2.4	19
Duck	9	1.3	1.8	19
Guinea-hen	12	0.8	2.8	19
Squab	9	1.1	2.1	19
Turkey	7	1.3	2.0	20
Bluefish	13	0.6	3.5	20
Halibut	16	0.7	3.3	20
Mackerel	15	1.0	2.5	20
Sardines in oil	7	1.4	1.6	20

VEGETABLES ALLOWED ON CARBOHYDRATE-FREE DIET

Asparagus	Endive	Sorrel
Brussels sprouts	Greens	Spinach
Cabbage	Kohl-rabi	String-beans
Cauliflower	Lettuce	Swiss chard
Celery	Pickles (sour)	Tomatoes
Cucumbers	Rhubarb	Water-cress
Egg-plant	Sauerkraut	

TABLE III.—Condensed Data from Cases of Diabetes Mellitus, which Show, by Periods, the Relation of the Caloric Value of the Diet to Maintenance, as Measured by the Nitrogen Equilibrium. The Daily Caloric Value of the Food was Approximately Constant during Each Period.

Patient.	Period days.	Glycosuria, Gm. per day.	Nitrogen per day, Gm.			Carbohydrate-free diet, calories per day.[3]	Calories per kilo per day.	Calories per sq. M per hour.
			Intake.	Output (urine and feces).	Balance.			
CASE 1.—Med. Hist., Nos. 36890 & 37408. Male, aged 38. Ht. 5 ft. 7 in. (170 cm.) Wt., 100 lbs. (45.4 Kg.). General condition very poor.	3	0	11.4	14.9	−4.5	1006	22.2	27.8
	4	0	16.1	17.9	−1.8	1503	33.1	41.6
	7	**0**	**17.9**	**16.7**	**+1.2**	**1704**	**37.5**	**47.2**[1]
	9	Tr.	**22.2**	**21.6**	**+0.6**	**2003**	**44.1**	**55.4**
			Two months later					
	9	6	15.6	16.7	−1.1	1504	33.1	41.6
	5	0	10.7	14.8	−4.1	950	20.9	26.3
	3	0	15.1	15.9	−0.8	1473	32.4	40.8
	14	**0**	**18.5**	**17.6**	**+0.9**	**1711**	**37.7**	**47.4**
	16	**0**	**18.9**	**17.7**	**+1.2**	**1984**	**43.7**	**54.9**
CASE 2.—Med. Hist., No. 36901. Female, aged 35. Ht., 5 ft. 6 in. (168 cm.). Wt. 111 lbs. (50.4 Kg.). General condition fair.	**4**	**45**	**17.6**	**16.1**	**+1.5**	**1487**	**29.5**	**39.7**
	2	**30**	**18.4**	**17.5**	**+0.9**	**1811**	**35.9**	**48.4**
	4	8	13.7	14.6	−0.9	1106	21.9	29.5
	3	0	4.6	9.0	−4.4	591	11.7	15.8
	2	0	14.5	15.8	−1.3	1182	23.5	31.6
	5	**0**	**20.0**	**14.4**	**+5.6**	**1750**	**34.7**	**46.7**
CASE 3.—Med. Hist., No. 37161. Male, aged 43. Ht., 5 ft., 10 in. (178 cm.). Wt., 110 lbs. (49.9 Kg.). General condition poor.	8	0	14.0	15.2	−1.2	1412	28.3	36.3
	3	0	11.4	15.5	−4.1	988	19.8	25.4
	3	**0**	**18.5**	**15.2**	**+3.3**	**1700**	**34.1**	**43.7**
	6	**0**	**19.4**	**17.9**	**+1.5**	**2104**	**42.2**	**54.1**
	1	0	7.4	13.8	−6.4	500	10.0	12.9
	2	**0**	**25.6**	**18.2**	**+7.4**	**2193**	**44.0**	**56.4**
CASE 4.—Med. Hist., No. 36776. Female, aged 56. Ht., 5 ft. 3½ in. (161 cm.). Wt., 132 lbs. (59.9 Kg.). General condition normal.	7	3	7.9	11.5[2]	−3.6	712	11.9	18.2
	4	**0**	**13.1**	**12.9**[2]	**+0.2**	**1133**	**18.9**	**29.0**
	3	0	1.6	5.5[2]	−3.9	49	0.8	1.3
	2	**0**	**11.6**	**11.4**[2]	**+0.2**	**1056**	**17.6**	**27.0**
	11	**0**	**15.1**	**11.9**[2]	**+3.2**	**1523**	**25.4**	**39.0**
CASE 5.—Med. Hist., No. 37488. Male, aged 26. Ht., 5 ft. 9 in. (175 cm.). Wt. 128 lbs. (58.1 Kg.). General condition fair.	**7**	**0**	**14.7**	**12.9**	**+1.6**	**1470**	**25.3**	**35.9**
	3	**0**	**20.0**	**14.1**	**+5.9**	**1943**	**33.4**	**47.4**
CASE 6.—Med. Hist., No. 37267. Male, aged 35. Ht., 5 ft., 7 in. (170 cm.). Wt. 120 lbs. (54.4 Kg.). General condition normal.	4	45	12.6	15.5	−2.9	1318	24.2	33.8
	3	22	10.2	14.7	−4.5	988	18.2	25.3
	5	0	5.4	10.9	−5.5	421	7.8	10.8
	4	**0**	**13.3**	**12.0**	**+1.3**	**1099**	**20.2**	**28.2**
	4	**0**	**15.9**	**13.6**	**+2.3**	**1465**	**26.9**	**37.5**
	8	**0**	**18.0**	**15.5**	**+2.5**	**1728**	**31.9**	**44.3**
CASE 7.—Med. Hist., No. 37261. Male, aged 41. Ht., 5 ft. 8 in. (173 cm.). Wt. 136 lbs. (61.7 Kg.). General condition normal.	6	5	15.6	23.6	−8.0	1503	24.4	36.1
	5	0	15.6	17.3	−1.7	1505	24.4	36.1
	3	0	17.0	17.1	−0.1	1614	26.2	38.7
	3	0	18.8	23.1	−4.3	1903	30.8	45.6
	3	**0**	**21.4**	**19.9**	**+1.5**	**2048**	**33.2**	**49.1**

TABLE III—*Continued*

Patient.	Period days.	Glycosuria, Gm. per day.	Nitrogen per day, Gm.			Carbohydrate-free diet, calories per day.[3]	Calories per kilo per day.	Calories per sq. M per hour.
			Intake.	Output (urine and feces).	Balance.			
CASE 8.—Med. Hist., Nos. 36887 and 37230. Male, aged 13. Ht., 4 ft. 11 in. (150 cm.). Wt., 75 lbs. (34.0 Kg.). General condition normal.	12	0	8.2	9.9	−1.7	609	17.9	20.9
	3	**0**	**13.4**	**10.8**	**+2.6**	**1152**	**33.9**	**39.5**
	2	Trace	12.6	16.9[2]	−4.3	1284	37.8	44.0
	5	0	7.4	10.9[2]	−3.5	595	17.5	20.4
	9	0	13.5	14.6	−1.1	1157	34.0	39.6
	6	0	14.9	15.3	−0.4	1449	42.6	49.7
	5	0	15.4	15.7	−0.3	1363	40.1	46.7
			Six weeks later					
	3	0	12.9	15.2	−2.3	1101	32.4	37.7
	6	**0**	**18.4**	**16.4**	**+2.0**	**1508**	**44.4**	**51.7**
	1	0	8.4	9.4	−1.0	620	18.2	21.2
	7	**0**	**21.7**	**19.0**	**+2.7**	**1686**	**49.6**	**57.8**
CASE 9.—Med. Hist., No. 36838. Female, aged 12. Ht., 5 ft. 1½ in. (156 cm.). Wt., 60 lbs. (27.2 Kg.). General condition poor.	1	0	5.9	13.4	−7.5	532	19.6	19.5
	8	0	8.5	9.9	−1.4	994	36.5	36.4
	7	0	7.0	8.0	−1.0	570	21.0	20.9
	11	Trace	8.7	9.9	−1.2	858	31.5	31.4
	4	0	5.8	8.5	−2.7	529	19.5	19.4
	8	0	8.6	8.8	−0.2	840	30.9	30.8
	2	0	4.6	9.5	−4.9	360	13.2	13.2
	11	0	8.6	9.9	−1.3	832	30.6	30.5

The nitrogen of the food was either calculated according to Atwater and Bryant's tables,[4] or actually determined by analysis. The correspondence between the two methods was close enough to justify the use of the values as given in the tables for the present purposes. The nitrogen of the food, urine and feces were all determined by the Kjeldahl method. Most of these patients were under strict supervision either in a small metabolism ward or in private rooms. Twenty-four cases were studied. Of these, only a few will be given in detail. The urinary glucose was estimated by Benedict's[5] modification of Fehling's solution, the acetone substances in the urine by Shaffer's[6] procedure, and the blood-sugar by the method of Lewis and Benedict[7] or that of Bang.[8]

[1] The figures printed in heavy type indicate periods in which a positive nitrogen balance was obtained; the figures in lighter print indicate the periods of nitrogen loss.

[2] In these instances the nitrogen of the feces was estimated as 10 per cent. of the nitrogen intake; the remaining figures represent actual determinations.

[3] Carbohydrate-free diets contain approximately the proportion of proteins, fats and carbohydrates given in Table I, with the exception of cases 8 and 9, in which the carbohydrate content of the food was somewhat higher.

[4] Atwater, W. O., and Bryant, A. P.: U. S. Department of Agriculture, Bull. No. 28, 1906.

[5] Benedict, S. R.: Jour. Am. Med. Assn., 1911, lvii, 1193.

[6] Shaffer, P. A.: Jour. Biol. Chem., 1908, v, 211.

[7] Lewis, R. C., and Benedict, S. R.: Jour. Biol. Chem., 1915, xx, 61.

[8] Bang, I.: Biochem. Ztschr., 1913, lvii, 300.

The number of calories of the protein-fat diet necessary to bring about nitrogen equilibrium was found to be slightly greater than, equal to, or considerably less than the total average caloric requirement of persons of the same age and sex as the diabetics.

TABLE IV.—Summary of Table III. Caloric Requirement Necessary to Produce Nitrogen Equilibrium in Cases of Diabetes Mellitus, as Compared to the Normal Metabolism of Individuals of the Same Age and Sex.

Case.	Age.	Sex.	General condition.	Calories per hour per square meter of body surface.			Caloric requirements necessary to establish N equilibrium as compared to normal metabolism.
				Highest at which N equilibrium was not obtained.	Lowest at which N equilibrium was obtained.	Normal metabolism.[1]	
1. Period 1	38	M.	Very poor	41.6	47.2	43.7	8 per cent. higher.
Period 2	..	..	....	41.6	47.4	43.7	8 per cent. higher.
2.	35	F.	Fair	31.6	39.7	40.6	Unchanged.
3.	43	M.	Poor	36.3	43.7	43.7	Unchanged.
4.	56	F.	Normal	18.2	27.0	36.0	25 per cent. lower.
5.	26	M.	Fair	....	35.9	43.7	18 per cent. lower.
6.	35	M.	Normal	33.8	28.2	43.7	28 per cent. lower.
7.	41	M.	Normal	45.6	49.1	43.7	12 per cent. higher.
8. Period 1	13	M.	Normal	49.7	39.5	54.9	28 per cent. lower.
Period 2	..	..	....	37.7	51.7	54.9	6 per cent. lower.
9.	12	F.	Poor	36.4			

Since it is known that "if a given subject's basal metabolism is more than 10 per cent. from the average, it may be regarded as abnormal, but cannot be proved abnormal unless the departure is at least 15 per cent.,"[2] it may be concluded that the amount of food demanded to result in a nitrogen balance is not greater, in any one of the present series of cases, than the upper limits of normal metabolism, but may be lower (Table IV). This finding for diabetics is in strict accord with that of E. Voit and Korkunoff, who demonstrated that under normal conditions, "if fat and meat be ingested together, the quantity of the latter necessary to establish nitrogenous equilibrium is reduced to between 1.6 to 2.1, the starvation minimum."[3]

[1] Basal metabolism according to F. C. Gephart and E. F. Du Bois (Arch. Int. Med., 1916, xvii, 902), plus 10 per cent. to allow for the specific dynamic action of the diet.

[2] Gephart, F. C., and Du Bois, E. F.: Arch. Int. Med., 1916, xvii, 906.

[3] Lusk, G.: Science of Nutrition, third edition, 1917, p. 254.

TABLE V.—Data from a Case of Diabetes Mellitus; Female, aged Eight Years, Nine Months; Height, 4 Feet, 8 Inches (142 cm.); Weight, 47 Pounds, 3 Ounces (21.4 Kg.). This Patient is Suffering from Severe Diabetes Mellitus, as Shown by the Very High D:N Ratio; at the Same Time Her Caloric Requirements Necessary to Establish Nitrogen Equilibrium are Very Low.

Date 1916.	Urine.					Blood-sugar, per cent.	Food.						N.[3] balance, Gm.	Calories utilized.[1]		
	Glucose, Gm.	Acetone bodies as β-oxy., Gm.	N, Gm.	D:N ratio.	Calories lost as glucose and β-oxy.		Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Alcohol, Gm.	Total calories.	N, Gm.		Total.	Per Kg.	Per sq. M. per hour.
June 20	75.6	....	....	..	280	0.49										
21	36.0	14.7	4.70	6.0	199	0.25	15.2	1.2	7.5	..	104	2.43	−2.51	0	0.0	0.0
22	41.6	19.7	8.64	2.9	243	0.25	28.3	2.1	16.5	5.5	242	4.53	−4.56	0	0.0	0.0
23	37.8	14.9	6.94	2.8	207	0.33	31.1	2.3	18.0	5.5	261	4.98	−2.46	54	2.5	2.3
24	17.8	7.9	6.50	2.7	102	....	44.0	4.0	0.0	5.5	256	7.04	−0.16	154	7.2	6.7
25	37.4	7.5	10.72	2.1	172	....	81.4	20.4	14.1	5.5	620	13.02	+1.00	448	20.9	19.5
26	26.8	5.8	7.82	1.0	105	....	70.0	28.2	19.1	5.5	666	11.20	+2.26	561	26.2	24.4
27	+5.8[2]	+4.2[2]	+3.74[2]	1.5	+41[2]	0.33	13.2	1.2	0.0	5.5	104	2.11	.....	0	0.0	0.0
28	47.4	7.7	8.51	3.6	210	0.34	48.5	15.4	19.1	5.5	316	7.76	−1.53	106	4.9	4.6
29	47.7	8.8	9.22	3.1	216	....	48.5	15.4	19.1	5.5	316	7.76	−2.24	100	4.6	4.3
30	17.7	6.7	5.11	3.4	96	0.27	13.2	1.2	0.0	5.5	104	2.11	−3.21	8	0.3	0.4
July 1	23.0	7.2	6.30	3.7	117	....	15.4	1.4	0.0	5.5	115	2.46	−4.09	0	0.0	0.0
2	52.9	5.7	8.13	4.1	221	....	65.1	29.7	19.1	5.5	660	10.42	+1.25	439	20.5	19.1
3	55.0	9.1	9.94	3.5	244	....	73.4	28.9	18.0	5.5	682	11.74	+0.63	438	20.4	19.0
4	64.5	13.1	10.53	4.4	298	....	93.9	43.8	18.0	5.5	905	15.02	+2.99	607	28.3	26.4
5	52.8	11.2	8.93	3.9	246	....	97.9	28.1	18.0	5.5	775	15.66	+5.16	529	24.7	23.0
6	54.2	11.5	16.55	2.1	252	....	90.5	46.3	18.0	5.5	914	14.48	−3.52	662	30.9	28.7
7	61.4	13.2	11.78	3.6	287	0.32	103.6	55.1	18.0	5.5	1049	16.58	+3.14	762	35.6	33.1

[1] The figures of these columns represent the total number of food calories, less the calories lost in the urine as glucose and β-oxybutyric acid.
[2] Urinary specimen incomplete on this day. [3] Ten per cent. of the nitrogen of the food is calculated as being excreted in the feces.

SUMMARY. FROM JUNE 20 TO JULY 6 INCLUSIVE, EXCEPTING JUNE 27

Total food calories	7985	Calories utilized per kilo per day	13.9
Total calories lost in urine	3215	Calories utilized per square meter per hour	12.9
Total calories utilized	4770	Total nitrogen lost, grams	7.85
Calories utilized per day	298	Nitrogen lost per day, gram	0.49

The case[1] detailed in Table V demonstrates at what a low level of metabolism a nitrogen balance may be obtained. This child was evidently an instance of "total diabetes." The D : N ratio was constantly in the neighborhood of 3.65 to 1, indicating that no carbohydrate, derived either from the small amount of ingested starch or from the protein, was utilized. Inasmuch as starch, whether preformed or derived from protein, has been considered the most efficient sparer of nitrogen, it is remarkable that in this patient nitrogen equilibrium could be effected on a diet of 19 calories per square meter per hour, which is only a fraction of the normal standard. (Boys twelve to thirteen years of age on such a diet may be considered to have normal standard of metabolism of 54.9 calories per square meter per hour; Gephart and Du Bois do not give any figures for the normal basal metabolism of girls.) On calculating the metabolism for the whole period of observation, it is noted that although only 0.49 gm. of nitrogen were lost per day, yet the food actually utilized amounted to only 13.9 calories per kg. per day, or 12.9 calories per square meter per hour. This remarkable effect of a low, pure protein-fat diet in conserving the body's nitrogen may be the reason for the fact that this emaciated child was able to "walk around and go riding" three months later, although she was still excreting large amounts of sugar. The present case is one of the rare instances in which a maximal D : N ratio did not prove to be a sign of immediate danger of impending death. The fluctuations manifested in the D : N ratio from day to day are similar to those noted in other cases, and may be explained by irregular periods of glucose excretion and retention and not necessarily through inefficiency in the management of the case.[2]

From the clinical point of view it is extremely important to know whether or not it is possible to restore the lost body tissue; in other words, cause an assimilation of nitrogen, on these diets. The generally accepted fact is that it is difficult to cause a prolonged deposition of protein on a protein-fat diet.[3] Strictly speaking, the carbohydrate-free diets used in diabetes as in the present report,

[1] This patient was studied in the pediatric clinic under Dr. J. Howland; the blood-sugar was determined by Harold L. Higgins.

[2] Mosenthal, H. O., and Lewis, D. S.: Bull. Johns Hopkins Hosp., 1917, xxviii, 187.

[3] Lusk, G.: Science of Nutrition, third edition, 1917, p. 255.

contain from 10 to 15 grams of starch derived from the vegetables. It is rather problematical what effect such a small amount of carbohydrate may have. In some instances there is no tendency for the body to assimilate nitrogen to any marked degree. This is exemplified in Case 1, Table III. This patient showed no appreciable rise in his slight positive nitrogen balance when the diet was increased after nitrogen equilibrium had once been obtained either in the first or second periods of study. On the other hand, some diabetics exhibit the ability to assimilate nitrogen while on "carbohydrate-free" diets. This may be noted in Table III; Case 2 retained 28 grams of nitrogen in five days; Case 4, 35 grams in eleven days; Case 5, 29 grams in ten days; Case 6, 34 grams in sixteen days, and one diabetic patient of this series whose protocol is not charted, retained 49 grams of nitrogen in seventeen days. It is perfectly apparent from these data that the diabetic may often build up body protein while on a carbohydrate-free diet.

A study of Tables III and IV reveals some apparent contradictions: In Cases 6 and 8 the highest caloric value of the food at which nitrogen equilibrium was not obtained is greater than the lowest value at which equilibrium was obtained. These inconsistent results are no more opposed to one another than the very varying heights of metabolism required to produce nitrogen equilibrium in the different cases (Table IV). What the specific reason for the caloric requirement is in each case is impossible to determine; it may be stated definitely, however, from the data of Case 1 (Tables III and IV), that these factors may have a tendency to remain constant although in some individuals they may vary as in Cases 6 and 8.

In Case 6, Table III, it is apparent that in the first two periods the nitrogen output is higher, with a lower nitrogen intake than it is in some of the subsequent periods. The same fact may be noted in Case 2, Table III. In both of these patients there was a considerable glycosuria, while this slight excess of urinary nitrogen manifested itself. It may have been that the caloric loss of the urinary sugar resulted in a greater destruction of protein, or it may be that these are mild examples of the very marked protein break-down and excessive amounts of urinary nitrogen at times found in diabetes, as

in the case of Geyelin and Du Bois.[1] In either event, it is certain that nitrogen equilibrium was established at a considerably lower caloric food level in Case 6 after the glycosuria had subsided. It must be distinctly recognized, however, that the glycosuria in itself, although very marked, need not result in an increased caloric demand to establish nitrogen equilibrium. This is well shown in the case detailed in Table V.

The discrepancy in Case 8 is well explained in Table VI, which gives a portion of the protocol in detail. In the first days a nitrogen balance was readily obtained on a diet of about 1000 calories. On November 19 a definite series of changes appeared. Each one of these variations in itself might not have been worthy of attention, but taking them together they showed that many of the metabolic processes were synchronously affected. The acetone and diacetic acids increased in the urine, as shown by the qualitative tests, a trace of glucose was found in the urine, the nitrogen excretion rose considerably, the nitrogen balance became negative, and the blood sugar increased, although the diet was scarcely changed for three days. All of these phenomena were evidently brought about by a "cold in the head" of so slight a nature that the patient himself scarcely complained of it, and the body temperature only rose to 99.8° F. on one day. All these symptoms promptly rectified themselves with the disappearance of this infection of minimal intensity, except one: the power to establish nitrogen equilibrium at the former low diet level was lost and remained so when the patient was tested out again six weeks later. It is well known that nervous shocks and the severer infections play havoc with the health of diabetics. That a very slight disturbance should have such far-reaching effects is worthy of consideration in the management of these cases.

A study of Tables III, IV and V shows that the general condition of the diabetic, that is, whether his state of nourishment be normal, fair, poor or emaciated, tends to have no direct bearing on the number of calories per square meter per hour required to establish nitrogen equilibrium.

[1] Geyelin, H. R., and Du Bois, E. F.: Jour. Am. Med. Assn., 1916, lxvi, 1532.

TABLE VI.—An Abstract from the Complete Protocol of Case 8 of Table III. Effect of a Slight "Cold" on Glycosuria, Acetonuria, Blood-sugar and Nitrogen Equilibrium in a Case of Diabetes Mellitus, Male, Aged Thirteen.

Date. 1916.	Urine.					Feces Nitrogen, Gm.	Output Nitrogen, Gm.	Balance Nitrogen, Gm.	Food.						Blood-sugar per cent.	Remarks.
	Volume C.c.	Glucose.	Acetone.	Diacetic acid.	Nitrogen, Gm.				Nitrogen, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate Gm.	Total calories.	Calories per sq. M. per hour.		
Nov. 16	1245	0	++	+	10.08	0.60	10.68	+0.15	10.83	67.7	54.3	31.3	911	31.2	0.10	
17	1070	0	+	+	8.67	0.60	9.27	+3.74	13.01	81.3	66.6	44.2	1134	38.9		
18	1670	0	+	+	11.86	0.60	12.46	+0.55	13.01	81.3	66.6	44.2	1134	38.9		
19	1260	0	++	+	9.95	0.60	10.55	+3.50	14.05	87.8	69.6	44.2	1188	40.7	....	Contracted slight "cold."
20	1605	Trace	+++	++	14.28	0.60	14.88	−0.82	14.06	87.9	85.5	44.2	1337	45.8	0.13	
21	1640	Trace	++	+	18.04	0.80[1]	18.84	−7.62	11.22	70.1	82.2	43.9	1232	42.2		
22	1260	0	++	+	7.28	0.80[1]	8.08	−5.44	2.64	16.5	0.9	18.0	150	5.1		
23	990	0	++	+	9.41	0.80[1]	10.21	−3.43	6.78	42.4	31.0	18.1	536	18.3	....	Maximal temperature, 99.8°.
24	1435	0	++	+	11.05	0.80[1]	11.85	−5.26	6.59	41.2	33.6	18.0	555	19.0	....	Temperature normal on all other days.
25	1870	0	++	+	10.29	0.80[1]	11.09	−2.00	9.09	56.8	52.8	18.0	798	27.3		
26	2620	0	++	+	12.31	0.91	13.22	−1.54	11.68	73.0	60.6	18.0	937	32.1		
27	2680	0	++	+	13.40	0.91	14.31	−2.13	12.18	76.1	66.3	18.0	1002	34.3		
28	1840	0	+	+	10.12	0.91	11.03	+1.71	12.74	79.6	66.6	18.0	1020	35.0		
29	2550	0	+	0	13.77	0.91	14.68	−0.54	14.14	88.4	64.6	20.3	1047	35.9		
30	2030	0	+	0	13.40	0.91	14.31	−1.61	12.70	79.4	80.9	18.0	1152	39.5		
Dec. 1	2360	0	++	0	13.92	0.91	14.83	−0.09	14.74	92.1	77.5	33.3	1235	42.3	0.09	
2	2300	0	++	0	13.34	0.91	14.25	−0.94	13.31	83.2	83.8	31.3	1249	42.8		

[1] Nitrogen contents of feces estimated, not determined.

Case 9 (Tables III and IV) is an instance of a patient in whom nitrogen equilibrium could not be established without the appearance of glucose in the urine. The treatment in this case was to continue the inadequate diet and maintain the urine in a sugar-free condition. The result has been a slow but evidently perceptible loss of weight and strength. Case 4 (Tables III and IV), a woman in good circumstances, has continued on the given diet for one year, attending to her social and household duties, and has gained strength and a little weight, although her diet is a low one. Case 5 (Tables III and IV) has taken the low diet indicated for an interval of six months; during this period he has solicited contracts for an engineering company, being on his feet nearly all the time, and feels perfectly strong and well. Case 7 (Tables III and IV) reports that he has taken the 2000-calory carbohydrate-free diet for a period of eight months, while he has been working as a farmer, and that his health and strength are good, though he has gained no weight. These few examples may serve to indicate (they are too few to prove the claim) that a diabetic need take only sufficient calories to result in a nitrogen equilibrium in order to bring about a maintenance of health and strength.

Conclusions. Diabetic patients may be established in nitrogen equilibrium by a carbohydrate-free diet having a caloric value equal to the standard total caloric requirement. In many instances, this may be accomplished at a considerably lower level of feeding. The factors which determine the dietary level at which a diabetic attains a nitrogen balance are apparently very numerous, and not fully determined; glycosuria at times, and infections, even of very slight degree, may necessitate a higher diet to bring about the desired result.

A marked assimilation of nitrogen may occur in diabetics while on a carbohydrate-free diet. The lowest diet which will conserve the physical and mental efficiency of the diabetic is that which maintains the nitrogen equilibrium of the patient. A rough estimate for clinical purposes of what constitutes a maintenance ration for the diabetic on a carbohydrate-free diet, is from 1500 to 2000 calories. In adjusting the value of the diet it should be borne in mind that women and small individuals generally require less food than men and larger individuals.

DISCUSSION ON THE PAPERS OF DRS. ALLEN, GRAY AND JOSLIN, FITZ, AND MOSENTHAL

Dr. Foster said that, looking back to the time ten years ago when there was practically no scientific work on this question, the profession may feel a little pardonable pride in the character of the work which is now being undertaken in so many parts of the country. But the American temperament is unfortunate, it seemed to him, in the tendency to make immediate application of every small scientific fact that may be disclosed before it has been linked up with the other facts which are already known.

However, let that be as it may, a good example of the high standard of work that is being done in many places, is this of Dr. Fitz; and the speaker wondered if perhaps those peculiar relations brought out in his paper between ketonuria and the ketones in the blood may not be explicable on the basis of a functional change in the kidney at the time when acidosis is developing. That is to say, that on account of some change in the kidney, ketone bodies no longer are excreted but accumulate in the tissues—a point thrown out not as fact but as possibly suggestive.

Then, with regard to the pathology of the pancreas in diabetes, Dr. Allen has been needfully careful in stating the facts as he has discovered them. It is notoriously an extremely knotty question to interpret the facts; and the speaker cannot see that we are at the present time in position to evaluate them. Dr. Allen has stated that certain pancreases are close to normal, certain others show gross changes. Now it is not fair, as a problem in pathology, to compare the pancreas from a diabetic patient with the pancreas of other cases that may come to autopsy. The conditions which lead up to the death in severe diabetes (and those are the only cases likely to give us the facts) are very peculiar. We have not only a severe nutritional disturbance, which gives rise to a peculiar blood state, but a blood condition which might in itself cause certain organic changes; so that if we are going to get facts, we must compare pancreases from diabetic patients with pancreases where something like the same conditions have obtained during life.

The speaker detected in Dr. Allen at the present time a little more conservative attitude apparently than he formerly took with regard to pathology. A few years ago he was very sure that diabetes is a *functional* disturbance: now, in some instances, it seems not to be so and he explains it as a pathological disturbance.

This kind of work must be done; these facts must be found out; the kind of work that Dr. Allen has at this meeting described must all be reviewed; but our interpretations must be extremely guarded. Because, as previously remarked; with our American tendency we immediately apply each little theory to our therapeutic principles. It would also appear that those of us who are studying diabetes make the fundamental mistake of

regarding diabetes as one disease, when there is, perhaps, but a single symptom (glucosuria) which is common to a number of different disturbances. There is certainly the greatest possible difference—clinically, physiologically, every possible way; there is no more resemblance between the ordinary diabetic of fifty years of age and the case of a diabetic child than there is between two different infectious diseases or between a metabolic disease and an infectious disease. In the speaker's view we make that mistake.

There is in this connection a point that Dr. Joslin has called attention to quite properly in the study of diabetic children. Glycosuria with a child does not of necessity mean that that child is diabetic in the sense in which we now employ the term. We call some cases renal diabetes; and to be on the safe side we institute diabetic treatment for a period of time and perhaps the disorder vanishes, as it occasionally does; but at no time during that period has that child shown any of the characteristics which the other child (whom we call a diabetic) has shown. There is none of the dyscrasia; unless the diet is so bad that the child wastes. One word regarding the prognosis in these cases of diabetes in children. The speaker may perhaps be pardoned for saying that he thinks he was the first who undertook, as an experiment, to find out if keeping a child or any young adult sugar-free over a long period of time, made any particular difference with the outcome of that disease. The speaker's experience is this: In no case of diabetes, in the sense that we all mean, even when, with the coöperation of the most intelligent parents, the most ideal conditions have prevailed, has there failed to ensue, as years went by, a gradual loss of all tolerance, the gradual approach to the condition where the glycosuria could be controlled only with the most stringent diets. In no case, as years went by, has growth been maintained, has nutrition (ordinary healthy nutrition) been preserved. Dr. Allen says that a pessimist should not treat diabetes. A pessimist should not treat any disease; but yet parents come to you with children, and they ask (as the speaker has many times been asked): "By the institution of this method of treatment will my child get well?" What are you going to answer? Is there any one of us bold enough to say that "By carrying on this treatment five years, or ten years, eventually your child is going to attain maturity and lead a happy life?" That is the answer. Further than that, the question is not medical: the question is philosophical—"What is life worth?"

Dr. Van Slyke, speaking from a knowledge of the work gained as a laboratory co-worker with Dr. Fitz, averred that the latter had undertaken a monumental study of the acetone bodies in diabetes, whereof the report just presented was only the beginning, although the result of some hundreds of determinations already made. There were several points on which the work had already yielded evidence of value, one being the question as to

whether or not diabetic acidosis is due to retained acids only, or may be due also to the acids which are excreted. Since the time of Magnus-Levy, the speaker believes there has been no refutation of the idea that it is only the retained acids that cause acid intoxication. If that were so, we should regularly find in the body, and presumably in the blood, of the patient suffering with diabetic acidosis an amount of these acids chemically equivalent to the alkali deficit. As a matter of fact, this is sometimes the case. Often one finds acetone bodies in the blood approximately equivalent to the drop of the bicarbonate below the normal level; but great deviations from this rule have been frequently encountered by Dr. Fitz. The fall in blood bicarbonate may be quite out of proportion to the rise in blood acetone bodies. The apparent explanation is that the oxybutyric and diacetic acids, after decomposing part of the blood bicarbonate, may be excreted as salts of sodium, calcium or potassium to some extent. In the latter case the alkaline reserve of the body is depleted by acids which have not been retained, but have been excreted. The speaker therefore thinks Dr. Fitz's results indicate that acids that are excreted as salts frequently assist the development of diabetic acidosis.

Dr. Jacobi said he disagreed with many experiences mentioned at this meeting and in the literature concerning the frequency of tuberculosis and of diabetes in the Hebrew race. It had gone into literature everywhere, and particularly, he believed, in Dr. Fishberg's book, that those two diseases are very rare among the Hebrews. The speaker had probably seen as many Hebrew patients as other physicians present; but his patients were, he believed, of a different class. For sixty years he had observed tuberculosis among the Hebrew poor, and for the past thirty years diabetes, particularly in the Hebrew poor. It had always been stated that diabetes was a very common disease among Hebrews, which may be possible; he credited the statement; but it is more fréquent among the poor than the rich; the literature, mainly the German, which referred to Carlsbad, twenty to thirty years ago, spoke of the rich Hebrews as being diabetics; indeed, many were observed in Carlsbad, because they were rich enough to go to Carlsbad. Contrary to oft-heard statements, asserting the rarity of tuberculosis among Hebrews, he averred that the disease is frequent among their poor. He made these declarations knowing they would get into print and thus tend to dispel these false beliefs. It is important that our statistics should be gently scrutinized and corrected. He made these points not as discussion, but simply as a memorandum to appear in print; so that somebody may take advantage of it when he is in need of a positive fact.

Dr. Allen said (closing) in reference to Dr. Foster's very kindly discussion, that his former statements concerning the hypothesis of a functional

disturbance of the islands in diabetes had been based upon the reports in the literature of diabetic patients dying with plenty of islands in the pancreas, and that this view was apparently supported by these several observations (appearing in his paper) of diabetes of severe type when the islands show very little change and when they do seem so full of normal-looking cells that all we can do is to assume some functional change. The speaker was trying to add to that view of the matter these recent observations, which seem to indicate that so long as this is so, the diabetes can in large measure be controlled on the principle of sparing a weakened function; that the symptoms in that type of patient may be cleared up and he may then develop a surprisingly high carbohydrate tolerance, at least for the time being; and apparently he need not die unless the time arrives when he has a very considerable, even extreme, reduction of island tissue in his pancreas.

As to the other possibilities, such as the question of blood changes and other influences which may act to produce this exhaustion, that is one place where the animal experiments can be of service. That is, it can be said from animal experiments that this particular lesion seems to be specific to diabetes as reproduced in animals. Control experiments prove that glycosuria produced by adrenalin, the Bernard puncture or other agencies, prolonged glycosuria and acidosis from phloridzin, lowering of the alkali reserve of the blood by feeding or injection of acids, and other physiological and pathological states, are not accompanied by the specific changes in the islands. This exhaustion and degeneration of cells apparently represents overstrain and break-down of the normal function of the islands, and the animal experiments seem to offer an opportunity to undertake the pathological study of human cases from this new view-point.

Of course, this involves something of a definition of diabetes; and the speaker is one who believes in the unity of diabetes. When there is sugar in the urine, if it is due to abnormal permeability of the kidney, for example, Dr. Allen believes the name should be renal glycosuria, feeling that many mistakes in the literature have crept in through using the word diabetes for the simple appearance of sugar in the urine, and going on the assumption that they were identical, when the two are not identical. Most forms of glycosuria, especially in animals, are not diabetic; and diabetes is known to exist without glycosuria. The distinction should be made between the actual condition and its mere symptoms. The differences in the course and character of different cases of diabetes can perhaps be looked upon as determined by the causes back of it. That is, chronic pancreatitis in an old person can give rise to a different picture of diabetes from what is seen in the other type that comes on very acutely in young persons. The differences could be explained by the different etiology, and the modifying influences of age and other factors. The position which the speaker held justified now is that diabetes is one thing; anatomically it is destruc-

tion, or physiologically it is impaired function, of the islands of Langerhans: that that is diabetes, and it is always diabetes. Nothing else is diabetes.

As to the prognosis, and the relation of the optimist as compared with the mere truth-teller, it must be remembered nobody has called this or any other dietetic treatment a cure of diabetes. Nothing of that sort has been stated in our publications. We believe that the new method controls the course better than has been done before, and that the patients not only live longer but also enjoy greater strength, comfort and usefulness.

Replying to an observation at this point by Dr. Jacobi that others had professed a cure, Dr. Allen said, that is a mistake; and that mistake should be corrected here or elsewhere. It is impossible to think of diet as curing diabetes; and the things the speaker presented today showed one reason for this, namely: the changes, sometimes demonstrably organic, accompanying the diabetes and of course not curable by diet. A young child with severe diabetes probably will never grow up, even if kept free from glycosuria and the ordinary symptoms; because the islands of Langerhans are a vital organ, and because their disturbance involves a specific disorder of nutrition which interferes with growth and normal development. Those things have certainly to be told, if you tell them the truth; but yet there is a big difference in the personal element; and he had seen patients killed prematurely and unnecessarily by an unnecessarily gloomy prognosis, with the inference that the child had to die and you might as well let it go. We can, however, say to parents that their child can live for an undetermined number of months and years; and, as his own personal conviction, he thought we might also say that the treatment is improving, that there is a prospect for more improvement, and with this improvement there is the possibility that even these patients may be saved. He believed the general outlook in diabetes is hopeful rather than hopeless. His effort with every patient was to keep him hopeful. The justification for hope is that patients actually live in tolerable condition until there is apparently a very extreme scarcity of island tissue. By protecting the weakened function from the overload represented by excessive fat and caloric intake and excessive body weight, which had been among the most important causes of so-called "spontaneous downward progress" in the past, it is possible for a considerable proportion of patients with milder diabetes to live out their normal lifetime with comfort and enjoyment.

He had at another place some slides of both animal and human pancreatic specimens, which he said he would be glad to show privately to such persons as might be specially interested in these changes. They ought to be seen by those who intend to look for such lesions; in fact, those who intend to look for them ought to work on experimental animals for preliminary experience. The changes will be passed over sometimes in human material unless the observer knows what to look for.

Dr. Joslin said that about 3 per cent. of his cases of diabetes had had tuberculosis, that 9 per cent. of all his cases were Hebrews, that 2 of the 30 fatal cases in Hebrews succumbed to tuberculosis, and finally, that 27 per cent. of the Jewish cases were hereditary in contrast to 21 per cent. for the total number of cases. Morrison (*Boston Med. and Surg. Jour.*, 1916, clxxv, 54) has looked up the statistics of diabetes for Boston for eighteen years. He found it was nearly twice and a half as common among Hebrews as compared with the other races in the city.

Dr. Mosenthal's contribution to this symposium is certainly valuable, because it brings exact data regarding the food which we are giving our patients and also shows the effect of it. I have just summarized the diets of three groups of cases of thirty patients each. The results are shown in the accompanying table:

The most successful treatment of diabetes in children seems to be to keep them sugar-free and upon a low diet, without attempting to have them gain weight until they have demonstrated that they can readily keep sugar-free upon the diet allowed. From an experience of eighteen years in treating diabetes in children, I can say that I have never seen a case where routine treatment has been renounced, but that the child has fallen into a worse condition than he would have been in had the prescribed regulations been followed straight through to the end.

Dr. Solis Cohen (closing) said, take a body of normal men, and another with a tendency to tuberculosis. Among the former a certain proportion will be susceptible to diabetes, using the term "diabetes" as Dr. Allen has done; and among the tuberculous a certain number will be found becoming diabetic; also among the diabetic, a certain number becoming tuberculous. But the incidence of tuberculosis among the diabetic will be less than among the community at large; and the incidence of diabetes among the tuberculous, likewise less than among the community at large. We find, however, that those who become diabetic among members of tuberculous families will have among their relatives quite a large number immune from tuberculosis but suffering with autonomic and endocrine disorders of various kinds. For instance, a man of tuberculous antecedents with diabetes has a son who is obese and who, until a month or two ago, at the age of fourteen, had undescended testicles, and many of whose characteristics are feminine. Examples could be multiplied. The speaker believed that there is some connection between diabetes and the endocrine disturbances and autonomic disturbances in the immune members of tuberculous families. In other words, the intermediate link between diabetic and tuberculous, normal and diabetic, is the endocrine disturbance associated with immunity, relative or complete, from tuberculosis.

The speaker was loth to differ with Dr. Jacobi. Yet, some twenty years ago or longer being called upon to deliver a lecture upon Jewish hygiene

Group.	Date.	Average number of days in hospital.	Weight in kilograms.				Average daily diet in hospital in grams.												Duration in years to Dec. 1, 1916.	Treatment begun with.		Acidosis.		
							First week.						Last week.									Present.		
			Entrance.	Lowest.	Exit.	Loss.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories.		Carbohydrate.	Protein.	Fat.	Alcohol.	Calories.			Fasting.	Exclusion of fat preparatory treatment.	Developed after entrance.	Decreased after entrance.	Absent during hospital stay.
											Total.	Per kilo.					Total.	Per kilo.						
I	April 6, 1915 to Mar. 18, 1916	33	60	56	57	3.07	19	17	11	2	243	4	26	54	76	1	992	18	5.8	12	18	7	15	8
II	Mar. 19, 1916 to July 19, 1916	23	59	56	56	2.87	25	24	6	1	234	4	43	60	82	4	1151	21	4.2	16	14	4	6	20
III	July 20, 1916 to Feb. 2, 1917	28	56	53	54	1.6	27	24	16	1	356	6	43	60	90	3	1239	23	4.0	6	24	2	12	16

before the Gratz College of Philadelphia, he had prepared therefor by a careful study of his private and dispensary practice as well as that of several friends who gave access to their records. He had found that among Jews diabetes was relatively common, both among rich and poor; while tuberculosis was rare among rich Jews. And though tuberculosis was frequently met among poor Jews and especially those of Russian birth or descent, even so, the proportion of tuberculosis among them was much less than among those of other races living under similar social and economic conditions. It is not an absolute immunity from tuberculosis that Jews exhibit—or Hebrews, if that term be preferred—but it is a relative immunity. Not a day passes but the speaker sees a half-dozen of his poorer brethren with tuberculosis; but the disease is less virulent. They last much longer and their proportion of sick to well is, after all, less than that of their neighbors of other descent, in the same degree of poverty.

A BRIEF EXPERIMENTAL STUDY OF THE MORPHOLOGY OF THE HEART MUSCLE FOLLOWING HYPOTHYROIDISM

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Slow action of the heart is one of the chief characteristic features of hypothyroidism whether occasional or continuous, spontaneous or operative. In some cases other aspects of the heart action give also the appearance of a myocardial disease. Thus exercise, though followed by dyspnea, may not be accompanied by commensurate increase in heart rate. The quality and vigor of the heart muscle tone is often greatly impaired and the valve closures are no longer clear and prompt. The capillary return, particularly in the periphery, is delayed, favoring fibrosis and diminishing parenchymatous activity.

The use of digitalis, camphor, caffein and similar drugs in most of these instances fails to improve these symptoms but even in long-standing cases, the giving of thyroid quickly relieves in large part inadequate heart action or now renders the action of the drugs effective.

A diagnosis of myocarditis, or more probably of myocardial degeneration would be a very natural conclusion in such instances were it not for the other signs of thyroid deficiency and the prompt relief of this among the other signs and symptoms of a defect which follows when thyroid is given.

Inasmuch as these cardiac signs appear quite early in hypothyroidism it is to be expected that whatever the basic cause be, it should become evident in the heart mechanism fairly soon. If the changes induced were of an anatomical nature, relief of any rapid degree in long-standing examples would not be expected following thyroid medication. In cases which give histories of thyroid instability, especially such as had at some time shown definite hypothyroidism, permanent signs and symptoms of muscle defect may, however, appear.

It is obvious that this question cannot be satisfactorily answered by the study of material taken from clinical cases of hypothyroidism or myxedema, for the literature in this respect shows great variation in reports as to the pathological anatomy of the heart, and it is obviously impossible to attribute to the thyroid deficiency alone the changes which are frequently reported in a condition which is accompanied by so many complicating problems as this.

From the clinical aspects of the condition there would appear to be but little doubt that the disease is brought about by chemical or physiological rather than by morphological defects, but to clear the ground and to decide certain questions in our own minds, preparatory to a broader study of the subject, we have undertaken the following brief study for the purpose of deciding whether or not the cardiac signs which appear in hypothyroidism are or are not accompanied by recognizable morphological alterations in the heart muscle. In a clinical study of a large group of hypothyroid conditions, now under way, this preliminary point appears to be of considerable importance.

For reasons of convenience, rabbits were selected for the study. The operation of thyroidectomy was very carefully performed under light ether anesthesia. Five deaths took place during or apparently as an immediate effect of the operation; these are not included in the study. All the visible thyroid tissue in the usual location was removed in each case, and an attempt was made to avoid the parathyroids. As tetany did not occur in any of the ten instances reported, it seems probable that we were successful in this respect.

In each case the material removed was examined microscopically to identify absolutely the character of the tissue. In all the ten

instances reported this was found to be only an apparently normal thyroid tissue.

After operation the animals were housed and fed as carefully as possible, and were under constant observation and expert care, though no great attempt was made to study them clinically. Immediately after death, if it occurred during the laboratory hours, the heart was removed and placed in a formalin fixative. A general autopsy was made in each instance and the apparent cause of death noted. When the animal died after laboratory hours it was placed at once in the ice-chest and was autopsied early the next day.

The hearts were examined grossly, fixed in formalin, and sectioned in paraffin. The sections were taken in each instance through the left ventricle vertically, through the tip of both ventricles, and a third plane extended tangentially through the interventricular septum. The sections were stained with hematoxylin and eosin, and were minutely studied under the customary powers of magnification.

EXPERIMENTS. Rabbit No. 2. Female operated June 26. Died August 8. Duration of postoperative life forty-three days, during which time the animal exhibited the customary signs of deficient thyroid secretion. It died with a septic peritonitis and a probable general septicemia.

Microscopic examination showed practically identical lesions in all sections. The most striking alteration consisted in a definite stain attraction on the part of the cell nuclei, with in some fibers a considerable ovoid area of granular degeneration at either pole of the nucleus. In a few instances a small amount of brownish pigment was found in this area. A certain amount of parenchymatous degeneration was demonstrable in nearly all fibers. About some of the capillaries and arterioles a leukocytic infiltration had taken place in some areas associated with some evidences of proliferation of the interstitial connective-tissue cells.

Rabbit No. 3. Male. Operated June 28. Some hemorrhage took place during and after the operation, but the animal lived until July 15, seventeen days, dying apparently from a septic peritonitis.

No consistent lesions were demonstrable in the heart fibers. Occasionally a typical nuclear proliferation was seen and some cells showed moderate albuminous degeneration. The interstitial and perivascular tissues showed a few small areas of cell proliferation and of small round-cell infiltration, clearly an acute change.

Rabbit No. 6. Male. Operated June 29. Slight oozing followed operation, but no vessels were cut. Respiration very rapid, reaching 120 per minute for about three-quarters of an hour. Died July 3, four days after the operation. At autopsy a bronchopneumonia was found, but no peritonitis or apparent wound infection. Coccidiosis of the liver was present.

Microscopic examination showed no change of a chronic nature in any part of the heart muscle, but in a few areas, notably in the interventricular septum, there was marked congestion of the capillaries and smaller bloodvessels, with some acute parenchymatous degeneration of the muscle cells.

Rabbit No. 7. Male. Operated June 29. Slight oozing. No vessels cut. Respiration shallow and rapid, 194 per minute. Cough was at first present, but the respirations soon fell to 120 and the cough disappeared. Animal died July 2, three days after operation. No gross lesions were apparent at autopsy.

Microscopic examination showed practically no lesions present, nothing which in any way could be considered as a result of the operation or of the thyroid defect.

Rabbit No. 9. Male. Operated July 3. Died July 16, thirteen days after operation. Autopsy showed a hemorrhagic area in the mediastinum. The inferior cava was engorged. Myocardium pale, bronchopneumonia, coccidiosis of liver, with cirrhosis. Suprarenals negative.

Microscopic examination showed no lesions present.

Rabbit No. 10. Operated July 3. Died July 6, three days after operation. Autopsy showed septic pneumonia, from which a pure culture of Bacillus coli communis was isolated.

Microscopic examination showed no changes whatever in the heart fibers but many of the capillaries and smaller venules were packed with blood cells in which a pronounced leukocytosis was apparent. Other blood channels were filled by the growth

of a bacillus corresponding morphologically to the Bacillus coli communis.

Rabbit No. 12. Male. Operated July 14. Died July 16, two days after operation. No lesions seen at autopsy. Wound apparently in good condition.

Microscopic examination shows marked congestion of many of the capillaries and venules of the myocardium, but no changes except an occasional muscle fiber showing parenchymatous degeneration.

Rabbit No. 13. Male, operated July 14. Died July 16, two days after operation. Autopsy showed no apparent lesions. Wound in good condition.

Microscopic examination shows absolutely no changes.

Rabbit No. 14. Male. Operated July 18. Died July 25, seven days after operation. Autopsy showed no obvious lesions present.

Microscopic examination showed no lesions except occasional parenchymatous degeneration.

Rabbit No. 15. Operated July 29. Moderate hemorrhage. Died June 30, one day after operation. Abdominal wall wet, but no demonstrable peritonitis; wound moist. No peritonitis or pneumonia.

Microscopic examination of the heart showed no lesions whatever except for occasional parenchymatous degeneration.

Although the amount of material presented in this study is small and the extent of time during which the animals lived insufficient (from two to but forty-three days), since it apparently corroborates the natural conclusions derived from the clinical study of these cases, we have felt that this line of investigation is no longer profitable.

Our conclusion may be summarized as that the cardiac signs and symptoms produced as a result of hypothyroidism are not due to morphological alterations in the heart muscle, nor does this status produce secondary anatomical variations of any characteristic degree or type in the heart muscle.

A STUDY OF URIC ACID IN GOUT*

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"Without uric acid, no gout," has been for many years a generally accepted dictum. And yet in spite of many investigations the relation of uric acid to gout has not been clearly established. In the diagnosis of gout by chemical means the same uncertainty exists. The uric acid may be increased in the blood and diminished in the urine, but the diagnostic value of these findings is doubtful. The development of new methods in biochemistry within the past few years permits a more thorough study of the factors governing the excretion of uric acid, and for this reason we have reinvestigated this subject.

Our studies on gout have been along the following four lines:

1. A comparison of the uric acid content of the blood in the gouty and in the non-gouty.
2. The results obtained by the intravenous injections of uric acid in the gouty and in the non-gouty.
3. A comparison of the exogenous output of uric acid by the gouty and the non-gouty in feeding experiments.
4. The functional condition of the kidneys in gout. (This will be published as a separate study.)

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I. THE URIC ACID CONTENT OF THE BLOOD

In 1913 Folin and Denis[1] introduced a colorimetric method for the determination of uric acid in small quantities of blood. Since our investigations were begun Folin has offered certain criticisms of his own method. Nevertheless, by its use data have been obtained which are of clinical interest in relation to gout. Different observers have used modifications of the Folin and Denis method, but their reported figures in general seem too high to be comparable with those obtained by the use of the original method. For this reason we have not quoted the work of these authors, but only that of those using the method described by Folin and Denis.

The Uric Acid Content of the Blood in Non-gouty Persons. Figures for the quantities of uric acid estimated by the Folin and Denis method in the bloods of 381 non-gouty persons have been collected from the literature.[2] In 314, or 82 per cent., the amounts of uric acid per 100 c.c. of blood ranged from 0.5 to 3 mg. Twenty of the latter number were normal persons, while the remainder represented cases of various organic disease, exclusive of gout, or cases with psychopathic conditions. Folin and Lyman[3] found 4 mg. of uric acid in the blood of a healthy man who gave a family history of gout. Whether or not this patient should be grouped

[1] Folin, O., and Denis, W.: A New Colorimetric Method for the Determination of Uric Acid in the Blood. Jour. Biol. Chem., 1913, 13, 469.

Pratt, J. H.: A Study of Uric Acid in the Blood in Gout by the Method of Folin and Denis. Tr. Assn. Am. Phys., 1913, 28, 387.

[2] Folin, O., and Lyman, H.: On the Influence of Phenylquinolin Carbonic Acid (Atophan) on the Uric Acid Elimination. Jour. Pharmacol. and Exper. Therap., 1913, 4, 539.

McLester, J. S.: Studies on the Uric Acid of the Blood and Urine, with Special Reference to the Influence of Atophan. The Archives Int. Med., 1913, 12, 739.

Folin, O., and Denis, W.: On the Uric Acid, Urea, and total Non-protein Nitrogen in Human Blood. Jour. Biol. Chem., 1913, 14, 29.

Folin, O., and Denis, W.: On the Creatinin and Creatin Content of Blood. Jour. Biol. Chem., 1914, 17, 487.

Kocher, A. R.: Ueber den Harnsäuregehalt des Blutes als Krankheitssymptom. Deutsch. Arch. f. klin. Med., 1914, 115, 380.

Adler, H., and Ragle, B.: A Note on the Increase of Total Nitrogen, and Urea Nitrogen in the Cerebrospinal Fluid in Certain Cases of Insanity, with Remarks on the Uric Acid Content of the Blood. Boston Med. and Surg. Jour., 1914, 171, 769.

Folin, O., and Denis, W.: The Diagnostic Value of Uric Acid Determinations in Blood. The Archives Int. Med., 1915, 16, 33.

Pratt, J. H.: Studies on the Uric Acid in the Blood in Gout. Am. Jour. Med. Sc., 1916, 151, 92.

[3] Folin, O., and Lyman, H.: See Footnote 2.

here as non-gouty is a question of doubt. The amounts of urea and non-protein nitrogen in the blood of this person were normal, so that there is no evidence for renal impermeability to other nitrogenous substances. Of the 156 psychopathic patients reported by Adler and Ragle[4] the blood of 38 contained from 2 to 4.5 mg. of uric acid per 100 c.c. The number in which more than 3 mg. was present is not stated. Whether or not any of the cases were gouty or nephritic is not reported.

The bloods of the remaining 67, or 17.6 per cent., of the 381 non-gouty persons contained from 3 to 10 mg. per 100 c.c. The diagnoses of these cases were:

I. Chronic nephritis with and without uremia.[5]
II. Arterial hypertension.[6]
III. Acute and chronic types of non-gouty and non-traumatic arthritis.[7]
IV. Chronic lead poisoning.[8]
V. Leukemia.[9]
VI. Malignancy.[10]
VII. Acute infections, especially lobar pneumonia.[11]
VIII. One case each of migraine,[10] of renal calculus,[12] without nephritis, of mitral stenosis,[13] and of puerperal toxemia[14] in which the condition of the kidneys is not stated.

[4] Adler, H., and Ragle: Boston Med. and Surg. Jour., 1914, 171, 769. See Footnote 2.

[5] Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, 4, 539. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, 14, 29. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, 115, 380. Folin, O., and Denis, W.: The Archives Int. Med., 1915, 16, 33. See Footnote 2.

[6] McLester, J. S.: The Archives Int. Med., 1913, 12, 739 See Footnote 2.

[7] Folin, O., and Denis, W. Jour. Biol. Chem., 1914, 17, 487. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, 115, 380 Folin, O., and Denis, W.: T e Archives Int. Med., 1915, 16, 33. Pratt, J. H.: Am. Jour. Med. Sc., 1916, 151, 92. See Footnote 2.

[8] Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, 4, 539. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, 14, 29. See Footnote 2.

[9] Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, 14, 29. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, 115, 380. See Footnote 2.

[10] Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, 115, 380. See Footnote 2.

[11] Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, 17, 487. Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, 115, 380. Folin, O., and Denis, W.: The Archives Int. Med., 1915, 16, 33.

[12] Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, 14, 29.

[13] Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, 4, 539.

[14] Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, 17, 487.

Obviously, the results obtained in the first three groups, which include nephritis and arthritis, are of most importance in determining the value of uric acid estimations in the blood as a means of differential diagnosis in gout. All cases of nephritis[15] or of arthritis[16] do not retain uric acid, in spite of the fact that in both conditions the blood may contain large amounts of non-protein nitrogenous substances. Whether or not nephritis was present in the cases of arthritis in which retention of non-protein nitrogen occurred in the blood, is not stated. Of 39 reported cases of non-gouty, non-traumatic arthritis[7] the blood uric acid varied between 1.2 and 2.7 mg. in 30, or 77 per cent., and from 3 to 7.6 mg. in 9, or 13 per cent. In 1 of these cases[17] the figures varied from 1.6 to 5 mg. and in another from 0.8 to 7.6 mg. Twenty, or 42 per cent., of 50 reported cases of nephritis[18] showed from 1 to 2.9 mg. of uric acid per 100 c.c. of blood, and 29, or 58 per cent., from 3.3 to 10 mg. All of the above patients were receiving a purin-free diet at the time of the blood examinations.

Using the methods of Folin and Denis, we have determined the uric acid and the total non-protein nitrogen in the blood of 8 non-gouty patients without clinical evidences of nephritis and in 1 case of advanced chronic nephritis. The findings are given in Table 1.

TABLE 1.—URIC ACID CONTENT OF BLOOD OF NON-GOUTY PATIENTS

Case.	Diagnosis.	Mg. uric acid per 100 c.c. blood.	Mg. non-protein nitrogen per 100 c.c. blood.	Diet of patient.
1	Dementia precox . . .	2.1	42	Purin-free
2	Dementia precox . . .	1.6 to 3.5	42	Purin-free
3	Senile dementia	0.8	39	Purin-free
4	Chronic nephritis, chronic arthritis	4.5	137	Purin-free
5	Chronic arthritis	2.2	. . .	Mixed
6	Chronic arthritis	2.4 to 3.3	32	Purin-free
7	Acute gonorrheal arthritis .	2.0	40	Mixed
8	Chronic arthritis	1.8	28	Purin-free
9	cirrhosis of the liver . . .	1.7	40	Purin-free

[15] Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, 14, 29.
[16] Folin, O., and Denis, W.: The Archives Int. Med., 1915, 16, 33.
[17] Pratt, J. H.: Am. Jour. Med. Sc., 1916, 151, 92.
[18] Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, 4, 539. McLester, J. S.: The Archives Int. Med., 1913, 12, 739. Folin, O., and Denis, W.: Jour. Biol. Chem., 1913, 14, 29. Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, 17, 487. Folin, O., and Denis, W.: The Archives Int. Med., 1915, 16, 33.

The case of nephritis gave a high value for the blood uric acid. One of the cases of dementia precox and 1 of chronic arthritis showed 3.5 and 3.3 mg. per 100 c.c. of blood, but on another examination less than 3 mg. were found. Our results agree with those collected from the literature and confirm the observation that the blood of the great majority of non-gouty persons contains less than 3 mg. of uric acid per 100 c.c.

The Uric Acid Content of the Blood in Gouty Patients. Of 49 reported cases of gout in which the uric acid in the blood was estimated by the method of Folin and Denis, 38, or 86.3 per cent.,[19] showed from 3.1 to 7.2 mg. per 100 c.c., and 6[20] from 1.7 to 2.8 mg. All but six of the patients were on a purin-free diet prior to the uric acid determinations. In these six the blood contained from 3.1 to 5.2 mg. of uric acid per 100 c.c. of blood. Chronic nephritis was diagnosed in but two[21] of the entire number of patients. In these the blood contained 3.1 to 5.7 mg. of uric acid. In 17 of the cases[22] the non-protein nitrogen in the blood was determined. Less than 36 mg. were found in 5, or 29.4 per cent., and 52 to 60 mg. in 2, or 11.8 per cent.

Using the methods of Folin and Denis, we have determined the uric acid and non-protein nitrogen content of the blood in the accompanying tabulated seven patients with gout (Table 2). All of these patients possessed tophi. Two were also suffering with chronic nephritis. The presence of nephritis was questionable in the other five patients, the only evidences being an occasional very slight trace of albumin or a scanty number of hyaline or finely granular casts. In one of the five patients cardiovascular disease was present.

More than 3 mg. of uric acid per 100 c.c. of blood were found in all cases. The non-protein nitrogen of the blood was increased definitely above 50 mg. per 100 c.c. in the two patients with nephritis. No relation was found to exist between the amount of uric acid and the quantity of non-protein nitrogenous substances in the blood.

[19] See Footnote 2.

[20] Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, 115, 380. Pratt, J. H.: Am. Jour. Med. Sc., 1916, 151, 92.

[21] Kocher, A. R.: Deutsch. Arch. f. klin. Med., 1914, 115, 380. Folin, O., and Denis, W.: The Archives Int. Med., 1915, 16, 33.

[22] Folin, O., and Lyman, H.: Jour. Pharmacol. and Exper. Therap., 1913, 4, 539. Folin, O., and Denis, W.: The Archives Int. Med., 1915, 16, 33.

TABLE 2.—URIC ACID CONTENT OF THE BLOOD IN GOUTY PATIENTS

Case.	Mg. uric acid per 100 c.c. blood.	Mg. non-protein nitrogen per 100 c.c. blood.	Diet of patient.
1*	5.1	....	Purin-free
	4.8	57.0	
2*	3.3	62.0	Purin-free
3	4.6	....	Purin-free
	3.5	53.0	
4	3.3	50.0	Purin-free
5	5.1	....	Purin-free
	4.3	39.0	
6	4.9	43.6	Purin-free
7	5.8	47.6	Mixed

* Patient had chronic nephritis.

A review of the literature[22] gives the same findings. The results obtained by our studies confirm the observations of previous writers[16] and show that although in the majority of gout cases there are increased amounts of uric acid in the blood, a large percentage do not have markedly increased quantities of other non-protein nitrogenous substances in their blood when on a purin-free diet.

We appreciate that the status of the method for estimating blood uric acid is unsettled. Nevertheless, on statistical evidence more than 3 mg. of uric acid per 100 c.c. of blood is a symptom of gout and is of especial importance when less than 50 mg. of non-protein nitrogen is present.

II. EFFECTS OF INTRAVENOUS INJECTIONS OF URIC ACID

We have studied the effect of the intravenous injection of 0.5 gm. of uric acid on the quantities of that substance in the blood and in the urine. The method of procedure was to obtain the endogenous level of uric acid in the urine after the patients had been on a purin-free diet. Then the injection was made. Quantitations of uric acid in the blood were made on samples taken a few minutes prior to the injection, four hours afterward, and then at twenty-four-hour periods. Estimations of the urinary uric acid were made in urine collected in several periods during the day of the injection and thereafter in urine collected for twenty-four-hour periods. The diet and analytical methods used are as follows:

Methods. Patients were placed on a purin-free diet at least seven days before the injections of uric acid were made. The diet consisted of bread, cauliflower, potatoes, rice, cornflakes, the cereal preparations of wheat, lettuce, cabbage, tapioca, jelly, cream, butter, cheese, eggs, and sugar.

For purposes of injection 0.5 gm. of uric acid was dissolved in 30 c.c. of distilled water with the aid of 1 gm. of piperazine. The solution was sterilized in the autoclave at 10 pounds pressure for five minutes. It was found that autoclaving the solution for fifteen minutes under a pressure of 20 pounds of steam did not decompose the uric acid. Uric acid in the blood was determined by the original method of Folin and Denis[1] or by their modified procedure.[23] Non-protein nitrogen was determined by either the original method of Folin and Denis[24] or by their later direct Nesslerization procedure.[25] Uric acid in the urine was quantitated by one of Folin's colorimetric methods:[26] In certain cases determinations were made with the uric acid phenol reagent by the method described in Folin's laboratory manual.[26] In other cases his uric acid reagent was substituted for the uric acid phenol reagent in this method. The latter reagent gives at times results which are slightly too high. Nevertheless, we found that after feeding sweetbreads the results obtained in the same persons with the uric acid phenol reagent were fully comparable to those obtained with the uric acid reagent. In the descriptive tables, methods employed to quantitate uric acid will be designated in a footnote as the original method, the uric acid reagent method, and the uric acid phenol reagent method.

Intravenous Injections of Uric Acid into Non-gouty Persons. Studies by previous observers on the excretion of uric acid in non-gouty persons after its intravenous injection are given in Table 3. The experimental subjects were all on a purin-free diet.

Table 3 shows that after the intravenous injections into five non-gouty persons the amounts of uric acid excreted varied. In 2 of the 3 cases of arthritis more uric acid was excreted than had been injected.

We have given five non-gouty persons intravenous injections of 0.5 gm. of uric acid. Three of these were insane persons, and two had chronic arthritis. No evidence of kidney lesions was present in these patients, although complete renal function studies were made on but one. The findings of the uric acid injection experiments are given in the following protocols:

[23] Folin, O.: Laboratory Manual of Biological Chemistry, New York, 1916.

[24] Folin, O., and Denis, W.: New Methods for the Determination of Total Non-protein, Urea and Ammonia in the Blood. Jour. Biol. Chem., 1912, 11, 527.

[25] Folin, O., and Denis, W.: Nitrogen Determinations by Direct Nesslerization. Non-protein Nitrogen in Blood. Jour. Biol. Chem., 1916, 26, 491.

[26] Folin, O., an Denis, W.: On the Colorimetric Determination of Uric Acid in the Urine. Jour. Biol. Chem., 1913, 14, 95.

TABLE 3.—PREVIOUS OBSERVATIONS ON THE EXCRETION OF INTRAVENOUSLY INJECTED URIC ACID BY NON-GOUTY PERSONS

Observer.	Diagnosis.*	Exogenous output of uric acid.		Duration in days of the exogenous output.	Amount of uric acid injected, Gm.
		Gm.	Per cent.		
Bürger and Schweriner[28]	1. Chronic arthritis	0.66	132	3	0.5
	2. Chronic arthritis	0.89	178	3	0.5
	3. Chronic arthritis	0.38	76	1	0.5
Umber and Retzlaff[27]	3. Normal . . .	0.40	80	4	0.5
	4. Normal . . .	0.47	95	2	0.5

* The urine findings were normal in all instances.

CASE 1.—J. M., Med. No. 5948, white, male, aged 32.

Diagnosis: Dementia precox.

The patient did not use alcohol. The physical examination was negative. Blood-pressure was 100 mm. systolic and 70 mm. diastolic. The urine examination was negative. Phthalein excretion was 60 per cent. in two hours. The patient was placed on a purin-free diet October 29, 1915.

Date.	Time of collection.	Urine.			Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 c.c.	Uric acid in Mg. per 100 c.c.	
Nov.							
1 to 2	9 to 9 A.M.	1570	0.50	1.20			
2 to 3	9 to 9 A.M.	1820	0.50	0.97			
3 to 4	9 to 9 A.M.	2810	0.61	1.26			
4 to 5	9 to 9 A.M.	3995	0.54	1.21			
5	9 A.M. to 12 N.	370	0.08				
	12.15 P.M.	....	....	....	....	3.50	0.5 gm. uric acid intravenously.
	12 N. to 4 P.M.	280	0.09				
	4.15 P.M.	....	....	....	....	2.90	
5 to 6	4 P.M. to 12 N.	935	0.43				
	12 N. to 12 N.	1215	0.54	0.98			
6	4.15 P.M.	....	....	....	42.00	2.10	
6 to 7	12 N. to 12 N.	2420	0.71	1.25			
7	4.15 P.M.	....	....	....	....	1.70	
7 to 8	12 N. to 12 N.	2550	0.66	1.37			
8	4.15 P.M.	....	....	....	....	2.50	
8 to 9	12 N. to 12 N.	2250	0.66	1.06			
9	4.15 P.M.	....	....	....	....	1.6	

Endogenous output of uric acid, November 2 to 5 = 2.15 gm.

Endogenous output of uric acid per day = 0.54 gm.

Per cent. of injected uric acid excreted = 82 per cent.

Uric acid determinations made by the original method.

Case 2.—E. S., Med. No. 5510. White, male, aged 41.

Diagnosis: Dementia precox.

The patient was not an alcoholic. The physical examination was negative. Blood-pressure was 140 mm. systolic and 95 mm. diastolic. The urine examination was negative. Phthalein excretion was 65 per cent. in two hours. The patient was placed on a purin-free diet on October 29, 1915.

Date.	Time of collection.	Urine.			Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 c.c.	Uric acid in Mg. per 100 c.c.	
Nov.							
1 to 2	9 to 9 A.M.	1595	0.71	1.77			
2 to 3	9 to 9 A.M.	2525	0.69	1.31			
3 to 4	9 to 9 A.M.	2415	0.78	1.50			
4 to 5	9 A.M. to 7 A.M.	2680	0.56	1.50			
5	7 A.M. to 9 A.M.	400	0.08	0.14			
	9 A.M. to 12 N.	180	0.09	0.13			
	12.15 P.M.	....	....	....	....	2.10	0.5 gm. uric acid intravenously.
	12 N. to 4 P.M	1180	0.31	0.31			
	4.15 P.M.	....	....	....	....	2.80	
5 to 6	4 P.M. to 12 N.	1585	0.65	1.05			
	12 N. to 12 N.	2765	0.96	1.36	....	1.20	Total amount for 24 hours.
6	4.15 P.M.	....	....	....	....	1.20	
6 to 7	12 N. to 12 N.	2505	0.93	1.60			
7	4.15 P.M.	....	....	1.70	....	1.70	
7 to 8	12 N. to 12 N.	3016	0.87	1.88			
	4.15 P.M.	....	....	....	42.00	2.50	
8 to 9	.....	1380	0.49	1.11			
9	4.15 P.M.	....	....	....	....	1.6	

Endogenous output of uric acid November 2 to 5 = 2.74 gm.

Endogenous output of uric acid per day = 0.69 gm.

Exogenous output of uric acid November 6 to 8 = 0.69 gm.

Per cent. of injected uric acid excreted = 138 per cent.

Uric acid determinations were made by the original method.

Case 3.—M. K., Med. No. 5708. White, female, aged 73.

Diagnosis: Psychoneurosis.

The patient was not an alcoholic. The physical examination was negative except for evidences of arteriosclerosis usual for the age. Blood-pressure was 130 mm. systolic and 65 diastolic. The urine contained the slightest possible trace of albumin with the heat and nitric acid tests, and enough pus to render it turbid in appearance. Phthalein excretion was 55 per cent. in two hours. The patient was placed on a purin-free diet on October 29, 1915.

Date.	Time of collection.	Urine.			Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 c.c.	Uric acid in Mg. per 100 c.c.	
Oct. 31–Nov. 1	7 A.M. to 7 A.M.	2035	0.32	0.59			
1 to 2	7 A.M. to 7 A.M.	1130	0.29	0.54			
2 to 3	7 A.M. to 7 A.M.	1384	0.36				
3 to 4	7 A.M. to 7 A.M.	1048	0.21	0.58			
4	7 A.M. to 10 A.M.	250	0.05				
	10 A.M. to 12 N.	264	0.06				
	12 N.	....	....	....	....	0.8	
	12 N.	....	....	....	....	....	0.5 gm. uric acid intravenously.
	12 N. to 4 P.M.	167	0.01				
	4 P.M.	....	....	....	....	2.9	
4 to 5	4 P.M. to 7 A.M.	920	0.32				
5	7 A.M. to 12 N.	340	0.19				
4 to 5	12 N. to 12 N.	1427	0.52	0.54			
5	4 P.M.	....	....	....	....	1.4	
5 to 6	12 N. to 12 N.	1590	0.40	0.57			
6	4 P.M.	....	....	....	39.2	0.8	
6 to 7	12 N. to 12 N.	1820	0.33	0.61			
7 to 8	12 N. to 12 N.	1350	0.32	0.56			

Endogenous output of uric acid November 1 to 4 = 1.18 gm.
Endogenous output of uric acid per day = 0.3 gm.
Exogenous output of uric acid November 5 to 6 = 0.32 gm.
Per cent. of injected uric acid excreted = 64 per cent.
Uric acid determinations were made by the original method.

Date.	Time of collection.	Urine.			Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Creatinin in Gm.	Non-protein N in Mg. per 100 c.c.	Uric acid in Mg. per 100 c.c.	
Sept. 16	.....	....	....	....	....	....	Purin-free diet begun.
23	.....	....	....	....	32.20	2.4	
Oct. 5–6	7 A.M. to 7 A.M.	2190	0.34	0.88			
6 to 7	.....	2810	0.28	0.99			
7 to 8	.....	1820	0.30	1.05			
8 to 9	.....	1575	0.32	0.98			
9	7 A.M. to 10 A.M.	440	0.03				
	1.20 P.M.	....	....	....	....	3.3	
	1.30 P.M.	....	....	....	....	....	0.5 gm. uric acid intravenously.
	10 A.M. to 12 N.	460	0.02	0.08			
	12 N. to 4 P.M.	440	0.10	0.17			
	6 P.M.	....	....	....	....	4.1	
9 to 10	4 P.M. to 7 A.M.	1050	0.26	0.53			
10	2 P.M.	....	....	....	....	3.9	
9 to 10	12 N. to 12 N.	2390	0.42	0.79	....	....	Total for 24 hours.
10 to 11	7 to 7 A.M.	1060	0.30	0.84			
11	2 P.M.	....	....	....	....	2.8	
11 to 12	.....	1715	0.33	0.89			
12	.....	....	....	....	....	2.9	

Endogenous output of uric acid October 6 to 9 = 1.24 gm.
Endogenous output of uric acid per day = 0.31 gm.
Exogenous output of uric acid October 10 = 0.11 gm.
Per cent. of injected uric acid excreted = 22 per cent.
Uric acid determinations were made by the original method.

CASE 4.—M. T. Mc., Med. No. 3415. White, female, aged 39.

Diagnosis: Chronic arthritis.

The patient's habits were good. Except for the joint changes of a chronic arthritis, the physical examination was negative. Blood-pressure was 103 mm. systolic and 85 mm. diastolic. The urine contained the slightest possible trace of albumin and a small amount of pus microscopically.

CASE 5.—W. H. K., Med. No. 5278. White, female, aged 29.

Diagnosis: Chronic arthritis.

The patient's habits were good. She had had chronic polyarthritis with occasional fairly acute exacerbations for the previous two years. The joints had never been either severely painful or tender. During the previous six months stiffness of the knees had prevented walking. Physical examination was negative except for the joints. There was limitation of motion and crepitation in all joints of the extremities. The elbows, wrists, finger-joints, knees, and joints of both halluces were enlarged, principally as the result of thickening of the periarticular tissues. Blood-pressure was 110 mm. systolic and 75 mm. diastolic. Urine examinations were negative except for a scant trace of albumin and a rare cast in one of the specimens. Phthalein excretion was 65 per cent. in two hours.

Date.	Time of collection.	Urine.		Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Non-protein N in Mg. per 100 c.c.	Uric acid in Mg. per 100 c.c.	
Oct. 31	.....	.....	.....	.....	1.8	Purin-free diet begun.
Nov.						
4 to 5	7 A.M. to 7 P.M.	830	0.57			
5 to 6	.....	850	0.63			
6 to 7	.....	740	0.56			
7 to 8	.....	830	0.47			
8	7 A.M. to 10 A.M.	350	0.01			
	10 to 12 N.	100	0.06			
	12 N.	.....	.....	.....	1.6	
	12.15 P.M.	.....	.....	.....	.....	0.5 gm. uric acid intravenously.
	12 N. to 2 P.M.	297	0.18			
	2 to 5 P.M.	205	0.13			
	4.15 P.M.	.....	.....	.....	2.5	
8 to 9	5 P.M. to 7 A.M.	297	0.19			
8 to 9	7 A.M. to 7 P.M.	1249	0.57			
9	7 A.M. to 12 N.	278	0.16			
	12.15 P.M.	.....	.....	27.9	1.5	
8 to 9	12 N. to 12 N.	1177	0.66			
9 to 10	7 A.M. to 7 A.M.	888	0.41			
10 to 11	7 A.M. to 7 A.M.	1210	0.55			
11 to 12	.....	1045	0.75			
12 to 13	.....	975	0.57			
13 to 14	.....	1170	0.61			

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid November 5 to 8 = 2.23 gm.

Endogenous output of uric acid per day = 0.56 gm.

Exogenous output of uric acid November 9 = 0.1 gm.

Exogenous output of uric acid November 12 = 0.19 gm.

Per cent. of injected uric acid excreted November 9 = 20 per cent.

Per cent. of injected uric acid excreted November 12 = 38 per cent.

Total per cent. of injected uric acid excreted = 58 per cent.

Uric acid determinations were made by the uric acid phenol reagent method.

A study of the foregoing protocols shows a bizarre behavior in the output of the injected uric acid. Case 2 is the only one in which it is definitely apparent that the output of the exogenous uric acid began within the first four hours after its injection. The output began within the first twenty-four hours in Cases 2, 3, 4 and 5. The excretion of the injected uric acid did not begin until during the second twenty-four-hour period after its administration in Case 1. In Case 5 the output of uric acid occurred in the first and fourth days following the injection. The excretion of the intravenously introduced uric acid was completed in from one to four days in all the above cases. In Case 1 determinations were stopped before the endogenous level in the urine had been reached. Thus there were great variations found both in the time of beginning and the duration of excretion of the injected uric acid.

The quantities of the intravenously injected uric acid which were excreted varied from 22 per cent. to 138 per cent. in the 5 cases. That a patient should excrete less than 100 per cent. of the amount of uric acid injected is explained by a loss occurring during the distribution throughout the body. Such a distribution must be necessarily undergone before the uric acid can reach the kidneys. As will be discussed later, other substances disappear from the blood after their intravenous injection. The output of more than 100 per cent. of the uric acid injected is only apparent. This is probably due to the variations commonly found in the daily endogenous amount of uric acid excreted. If the endogenous excretion has been low prior to the injection, and for the first few days following intravenous administration a higher endogenous output in the urine should be present, then the addition of a considerable amount of exogenous uric acid derived from that injected would make an apparent excretion of more than 100 per cent. It is to be noted that 0.1 gm. represents 20 per cent. of the amount of uric acid which was injected.

Our findings in the urine after the intravenous injection of uric acid into persons without gout show: (1) that the excretion may occur at irregular intervals; (2) that the starting of the excretion usually varies from a few hours to twenty-four hours; (3) that the percentage excreted ranges from very little to very much; and (4)

that the duration of the output of injected uric acid is often protracted over several days.

The quantities of uric acid found in the blood after its intravenous injection varied in the different cases. In Case 1 no increase in the blood uric acid followed the injection. There was considerable fluctuation in the amounts present in this case. An increase in the blood uric acid was found four hours after the injection in Cases 2, 3, 4 and 5. This increase disappeared within the first twenty-four hours in Cases 2 and 5, but not until the second twenty-four hours after the injection in Cases 3 and 4.

Definite time relations between the disappearance of uric acid from the blood and its excretion in the urine cannot be established for non-gouty individuals from a study of the tables showing our results.

Intravenous Injections of Uric Acid into Gouty Persons.—Prior to our investigations, Umber and Retzlaff[27] had studied the output of intravenously injected uric acid in four patients with gout. In three the kidneys were stated to be normal. The percentages of uric acid excreted by these three patients were none, 8.6 per cent. and 24 per cent. within from one to two days. In their fourth case of gout the patient had "beginning albuminuria." In this case 23.6 per cent. of the injected uric acid was excreted within the first twenty-four hours. The results of this test in 4 cases have been published by Bürger and Schweriner.[28] One retained all the uric acid. The urine of this patient was free from albumin and casts. In the other cases small amounts were excreted. The urine of only one of these patients contained albumin and casts.

We have given four patients with gout intravenous injections of 0.5 gm. of uric acid. One patient had a severe type of nephritis. Of the others one showed no signs of nephritis and two such slight symptoms of that disease that kidney lesions could not be definitely diagnosed. The condition of the kidneys in these cases will be dis-

[27] Umber and Retzlaff: Zur Harnsäure-Retention bei der Gicht. Verhandl. d. Kong. f. inn. Med., Wiesbaden, 1910, 27, 436.

[28] Bürger, M., and Schweriner, F.: Ueber das Verhalten intravenous einverleibten Glykokolls bei gesunden und krankheiten Menschen (mit besonderer Berücksichtigung der Gicht und Lebercirrhose). Arch. f. exper. Pathol. u. Pharmakol., 1913, 74, 353.

cussed in another communication on the study of the renal function in gout. The findings in the blood and urine after the uric acid injections are given in the following protocols.

CASE 6.—D. J. T., Med. No. 2963. White, male, aged 55.

Diagnosis: Acute and chronic gout; arteriosclerosis; chronic nephritis; hypertension; chronic myocarditis; angina pectoris.

The patient had used one pint of rum a day for many years. He had had five attacks of typical podagra in the metatarsophalangeal joint of the right hallux during the previous fifteen years. One attack occurred while he was under observation in the hospital. Physical examination showed that the heart was enlarged to the left. The radial artery walls were tortuous and sclerotic. Blood-pressure was 184 mm. systolic and 140 mm. diastolic. The urine contained a trace of albumin and an occasional cast. Phthalein excretion was 5 per cent. in two hours.

Date.	Time of collection.	Urine.		Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Uric acid in Mg. per 100 c.c.	Non-protein N in Mg. per 100 c.c.	
1915						
June 26	.....	.....	.....	3.5	68.6	Purin-free diet begun.
July						
1 to 2	7 A.M. to 7 P.M.	550	0.07			
2 to 3	.....	590	0.07			
3 to 4	.....	620	0.10			
4 to 5	.....	435	0.13			
5 to 6	.....	1060	0.33			
6 to 7	.....	985	0.33			
7 to 8	.....	1010	0.33			
8 to 9	.....	760	0.38			
9 to 10	.....	710	0.25			
10 to 11	.....	890	0.27			
11 to 12	.....	570	0.20			
12 to 13	.....	865	0.27			
13	1 P.M.	.....	.....	3.1		
	1 P.M.	.....	.....	.....	.....	0.5 gm. uric acid intravenously.
	5 P.M.	.....	.....	4.9		
13 to 14	7 A.M. to 7 A.M.	950	0.47			
14	11 A.M.	.....	.....	4.1		
14 to 15	7 A.M. to 7 A.M.	935	0.35			
15	11 A.M.	.....	.....	4.7		
15 to 16	7 A.M. to 7 A.M.	660	0.17			
16	11 A.M.	.....	.....	2.9		
15 to 17	7 A.M. to 7 A.M.	923	0.35			
17 to 18	7 A.M. to 7 A.M.	994	0.34			

Endogenous output of uric acid July 5 to 13 = 2.36 gm.
Endogenous output of uric acid per day = 0.3 gm.
Exogenous output of uric acid July 14 to 15 = 0.22 gm.
Per cent. of injected uric acid excreted = 44 per cent.
Uric acid determinations were made by the original method.

CASE 7.—W. P. G., Med. No. 5471. Negro, male, aged 43.

Diagnosis: Gout; questionable chronic nephritis.

The patient's habits were good. During the last ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers. On physical examination numerous tophi were found in the ears and about the finger-joints. Otherwise physical examination was negative. The blood-pressure was 135 mm. systolic and 95 diastolic. The urine contained no casts, no blood and no epithelium. A scant trace of albumin was found once in the examination of several urine specimens. Phthalein excretion was 42 per cent. in two hours.

Date.	Time of collection.	Urine.		Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Uric acid in Mg. per 100 c.c.	Non-protein N in Mg. per 100 c.c.	
1916 Oct.						
21 to 22	7 A.M. to 7 A.M.	1300	0.57	.....	.....	Purin-free diet begun.
22 to 23	.....	1165	0.52			
23	.....	.....	.....	3.3	43.5	
23 to 24	.....	730	0.37			
24 to 25	.....	705	0.41			
25 to 26	.....	880	0.41			
26 to 27	.....	990	0.37			
27	7 A.M. to 10 A.M.	115	0.05			
	10 A.M. to 12 N.	90	0.03			
	12 N.	.....	.....	4.1		
	12.15 P.M.	.....	.....	.....	.....	Intravenously 0.5 gm. uric acid.
	12 to 2 P.M.	95	0.04			
	4 P.M.	.....	.....	5.1		
	2 to 5 P.M.	180	0.07			
27 to 28	5 P.M. to 7 A.M.	430	0.21			
		910	0.44	.....	.....	Total amount for 24 hours.
28	4.15 P.M.	.....	.....	4.3		
28 to 29	7 A.M. to 7 A.M.	905	0.41			
29 to 30	.....	625	0.28			
30 to 31	.....	840	0.39			
31 Nov. 1	.....	1030	0.59			
1	.....	.....	.....	.....	.....	Mild attack of gout.
1 to 2	.....	890	0.62	.....	.....	Mild attack of gout.
2 to 3	.....	1350	0.59			
3 to 4	.....	1030	0.51			
4 to 5	.....	1035	0.53			
9	.....	.....	.....	4.3	49.5	

Endogenous output of uric acid October 24 to 27 = 1.56 gm.

Endogenous output of uric acid per day = 0.39 gm.

Exogenous output of uric acid October 28 to 29 = 0.07 gm.

Per cent. of injected uric acid excreted = 14 per cent.

Uric acid determinations were made by the uric acid phenol reagent method.

CASE 8.—J. G., Med. No. 5421. White, male, aged 43.

Diagnosis: Gout; arteriosclerosis; hypertension; chronic myocarditis; very questionable chronic nephritis.

The patient had used beer freely. He had about sixteen attacks of severe polyarthritis of gouty character during the previous twenty-six years. Physical examination showed numerous tophi in the ears and on the fingers. The joints showed the changes of chronic arthritis. The radial artery walls were sclerosed. The blood-pressure was 185 mm. systolic and 117 mm. diastolic. Otherwise physical examination was negative. The urine examinations were negative. Phthalein excretion was 52 per cent. in two hours.

Date.	Time of collection.	Urine.		Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Uric acid in Mg. per 100 c.c.	Non-protein N in Mg. per 100 c.c.	
1916						
Oct. 10	.....	.....	.....	6.4	.....	Mixed diet.
11	.....	.....	.....	.....	.....	Purin-free diet begun.
13	.....	.....	.....	.....	.....	Acute attack of gout.
15 to 16	7 A.M. to 7 A.M.	1005	1.00	.....	.....	Acute attack of gout.
16 to 17	.....	960	1.01	.....	.....	Acute attack of gout.
17	.....	.....	.....	5.4	.....	Acute attack of gout.
17 to 18	.....	1260	0.71	.....	.....	Acute attack of gout.
18 to 19	.....	1230	0.96	.....	.....	Acute attack of gout.
19 to 20	.....	Lost	.....	.....	.....	Acute attack of gout.
20 to 21	.....	930	0.89	.....	.....	Acute attack of gout.
21 to 22	.....	905	0.68	.....	.....	Acute attack of gout.
22 to 23	.....	1370	0.78	.....	.....	Acute attack of gout.
23 to 24	.....	1355	0.80			
24 to 25	.....	870	0.44			
25 to 26	.....	830	0.70	.....	.....	Attack subsided.
26 to 27	.....	870	0.69			
27 to 28	.....	840	0.71			
28 to 29	.....	700	0.47			
29 to 30	.....	670	0.41			
30	12 N.	.....	.....	4.1		
	12.15	.....	.....	.....	.....	0.5 gm. uric acid intravenously.
	7 A.M. to 10 A.M.	105	0.08			
	10 A.M. to 12 N.	74	0.05			
	12 N. to 2 P.M.	171	0.11			
	2 to 5 P.M.	106	0.08			
	4.15 P.M.	.....	.....	4.6		
30 to 31	5 P.M. to 7 A.M.	330	0.22			
		786	0.52	.....	.....	Total amount for 24 hours.
31	12.15 P.M.	.....	.....	4.8		
Oct. 31–Nov. 1	7 A.M. to 7 A.M.	820	0.51			
1 to 2	.....	930	0.49			
2 to 3	.....	950	0.63			
3 to 4	.....	750	0.61			
4 to 5	.....	670	0.46			
6	.....	.....	.....	4.0	38.4	
Dec. 7	.....	.....	.....	4.3	39.0	

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid October 21 to 30 = 6.57 gm.

Endogenous output of uric acid per day = 0.66 gm.

Exogenous output of uric acid October 31 to November 5 = 0.

Uric acid determinations were made by the uric acid phenol reagent method.

Case 9.—A. L. E., Med. No. 5297. White, male, aged 48.

Diagnosis: Gout; cirrhosis of the liver; questionable nephritis.

The patient had used large quantities of beer and whisky for many years. In the previous five years the patient had had five attacks resembling more the exacerbations of a chronic arthritis than gout. Three of these attacks occurred in the Peter Bent Brigham Hospital. Physical examination showed several tophi in the ears. The joints of the hands showed some periarticular thickening. The radial arteries were palpable. Blood-pressure was 156 mm. systolic and 96 mm. diastolic. The liver edge was palpable 4 cm. below the right costal margin. Otherwise the physical examination was negative. The urine showed occasionally a scant trace of albumin and a few casts. Phthalein excretion was 24 per cent. in two hours.

Date.	Time of collection.	Urine.		Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Uric acid in Mg. per 100 c.c.	Non-protein N in Mg. per 100 c.c.	
Oct. 14	.....	.....	.....	.....	.....	Purin-free diet begun.
15	.....	.....	.....	4.6	.....	Acute gout.
16 to 17	7 A.M. to 7 A.M.	850	0.94	.....	.....	Acute gout.
17 to 18	.....	750	0.93	.....	.....	Acute gout.
18 to 19	.....	550	0.55	.....	.....	Acute gout.
19 to 20	.....	Lost				
20 to 21	.....	590	0.48	.....	.....	Mild acute gout.
21 to 22	.....	480	0.44	.....	.....	Mild acute gout.
22 to 23	.....	630	0.51	.....	.....	Mild acute gout.
23 to 24	.....	430	0.33	.....	.....	Mild acute gout.
24 to 25	.....	870	0.36	.....	.....	Mild acute gout.
25 to 26	.....	785	0.52	.....	.....	Mild acute gout.
26 to 27	.....	1040	0.54	.....	.....	Mild acute gout.
27 to 28	.....	1100	0.78	.....	.....	Mild acute gout.
28 to 29	.....	720	0.38	.....	.....	Mild acute gout.
29 to 30	.....	785	0.49	.....	.....	Mild acute gout.
30 to 31	.....	525	0.35	.....	.....	Mild acute gout.
31 Nov. 1	.....	785	0.52	.....	.....	Mild acute gout.
1 to 2	.....	710	0.44			
2 to 3	.....	475	0.35			
3	7 A.M. to 10 A.M.	42	0.04			
	10 A.M. to 12 N.	67	0.05			
	12 N.	.....	.....	3.5		
	12.15 P.M.	.....	.....	.....	.....	0.5 gm. uric acid intravenously.
	12 N. to 2 P.M.	31	0.03			
	2 to 5 P.M.	57	0.06			
	4.15 P.M.	.....	.....	5.7		
3 to 4	5 P.M. to 7 A.M.	219	0.18			
		416	0.37	.....	.....	Total amount for 24 hours.
4	.....	.....	.....	5.1	52.6	
4 to 5	7 A.M. to 7 A.M.	218	0.20	.....	.....	Questionable loss of one voiding of urine.
5 to 6	.....	550	0.40			
6 to 7	.....	355	0.19			
7 to 8	.....	400	0.28			
8 to 9	.....	480	0.32			
9 to 10	.....	460	0.29			
10 to 11	.....	485	0.29			
14	.....	.....	.....	4.1		

The daily output of uric acid was too variable to permit an accurate determination of an average endogenous level.

Endogenous output of uric acid October 21 to November 3 = 6.42 gm.

Endogenous output of uric acid per day = 0.46 gm.

Exogenous output of uric acid November 4 to 11 = 0.

Uric acid determinations were made by the uric acid phenol reagent method.

A study of the foregoing protocols shows that in Case 6, of nephritis, 44 per cent. of the injected uric acid was excreted. It will be noted that from July 2 to 4 the daily excretion of uric acid in this case was less than 0.1 gm., while a few days later it had risen to more than 0.3 gm. Case 7, without evidences of nephritis, put out 14 per cent. of the uric acid injected. In Cases 8 and 9 the daily excretion of uric acid was too variable to permit the calculation of an average endogenous level with accuracy. There was, however, no apparent rise above the endogenous output after the intravenous injections. There is a question as to whether one voiding of urine was lost the second night following the uric acid injection in Case 9. The variability in the endogenous excretion of uric acid in these 2 cases, 8 and 9, is connected with the gouty attacks which occurred during the periods of observation. Comparable findings were obtained in another case of gout with tophi, not included here, in which we studied the uric acid excretion during an acute attack. A very mild gouty attack occurred the night of the sixth day following the injection of uric acid in Case 7. These findings confirm the observation of Brugsch and Schittenhelm[29] who reported that in the same cases of gout there were periods of low and periods of high endogenous uric acid excretion.

A study of the tables shows that the amounts of uric acid[30] found in the blood in different cases of gout while on a purin-free diet varied from 3.1 to 4.1 mg. per 100 c.c. Higher values than these were present in Cases 8 and 9 during acute attacks and at a time when the patient, Case 8, was receiving a mixed diet. An increase in the blood under these two conditions has been pointed out by one of us.[31] In all of the cases a rise of from 0.5 to 1.8 mg. of uric acid was present in the blood four hours after the intravenous injection of uric acid. This increase in blood uric acid persisted for forty-eight hours or longer in 3 of the cases (6, 8 and 9). In the remaining case (7) it disappeared within the first twenty-four hours. Three of these patients with gout retained the increase of uric acid in the

[31] Pratt, J. H.: Studies on the Uric Acid in the Blood in Gout. Am. Jour. Med. Sc., 1916, 151, 92.

[29] Brugsch, T., and Schittenhelm, A.: Zur Stoffwechselpathologie der Gicht III Mittheilung. Ztschr. f. exper. Path. u. Therap., 1907, 4, 480.

[30] By uric acid in the blood we mean the substance determined by the colorimetric method of Folin and Denis.

blood twenty-four hours longer after the injection than did any of the non-gouty patients.

Summary of the Results Obtained by the Intravenous Injections of Uric Acid. Nine patients, five without gout and four with gout, have been given 0.5 gm. of uric acid intravenously. Determinations of the amounts of uric acid in the blood have shown a small but definite increase four hours after the injection in eight of the patients. From these findings it would seem highly probable that by the methods employed the substance quantitated in the blood after the intravenous injections was really uric acid. The increase in blood uric acid resulting after injection of uric acid disappeared within forty-eight hours after the injection in four non-gouty and one of the gouty patients (Case 7). In the remaining 3 cases of gout it still persisted at the end of forty-eight hours.

The five non-gouty patients excreted from 22 per cent. to 138 per cent. of the uric acid injected. Of the 4 cases of gout the 1 with nephritis put out 44 per cent. of the uric acid injected, while very little or none was excreted by the other 3. These findings show that the failure to excrete a large percentage of uric acid after uric acid injections (exogenous uric acid) is not a pathognomonic symptom of gout, although it would seem to occur more frequently in gouty than in non-gouty persons.

We have followed the method adopted by previous writers in computing the output of exogenous uric acid, to make our findings comparable with theirs. The method has been to determine the average daily endogenous uric acid excretion prior to the administration of purin-containing substances. After the injection or feeding of purin-containing materials all outputs in excess of the previously determined average endogenous output have been considered as exogenous uric acid.

This generally accepted method of calculation is often open to criticism. The daily outputs of endogenous uric acid are somewhat variable. It would probably be more correct to consider as exogenous uric acid only those outputs whose amounts are in excess of the maximum endogenous output. Otherwise one cannot be sure that a certain amount of what is really endogenous uric acid has not been included in the portion computed as exogenous uric acid. We have calculated the exogenous output after the intra-

venous injections of uric acid in our cases on this basis and the results are given in Table 4. For purposes of comparison the exogenous outputs as determined by the generally accepted method are also given.

TABLE 4.—RESULTS OBTAINED BY THE TWO METHODS OF CALCULATING EXOGENOUS URIC ACID OUTPUT

Case.	Average daily endogenous output of uric acid in Gm.	Exogenous uric acid output.		Maximum daily output of endogenous uric acid in Gm.	Exogenous output of uric acid exceeding maximum daily endogenous output.	
		Gm.	Per cent.		Gm.	Per cent.
1	0.54	0.41	82	0.61	0.20	40
2	0.69	0.69	138	0.78	0.42	84
3	0.30	0.32	64	0.36	0.20	40
4	0.31	0.11	22	0.34	0.08	16
5	0.56	0.29	58	0.63	0.15	30
6	0.30	0.22	44	0.38	0.09	18
7	0.39	0.07	14	0.41	0.03	6
8	0.66	0	0	0.89	0	0
9	0.46	0	0	0.78	0	0

Considering as exogenous uric acid only those outputs which exceeded the maximum endogenous excretion gives lower figures for the percentages of uric acid excreted. By this method of calculation the anomalous exogenous excretion of 138 per cent. in Case 2 drops to the reasonable figure of 84 per cent. The excretion of 44 per cent. of exogenous uric acid by gout Case 6 becomes 18 per cent. by this method of calculation, which is a more reasonable amount in a case of gout with nephritis of severe type.

III. EXOGENOUS URIC ACID EXCRETION AFTER THE FEEDING OF PURIN- OR NUCLEIN-CONTAINING SUBSTANCES

We have studied the exogenous uric acid excretion after feeding sweetbreads to a patient with chronic arthritis and to two with gout. Previous observers have employed the results obtained by studies on the excretion of exogenous uric acid (1) as a basis for theories relating to the etiology of gout, and (2) as an aid in the diagnosis of that disease. It is generally accepted that gouty patients eliminate less exogenous uric acid than do normal persons. But whether or not this phenomenon is of diagnostic importance

is not well established. Certainly there is much controversy regarding the role of uric acid in the etiology of gout.

For purposes of comparison we have tabulated from the literature figures for the output of exogenous uric acid derived from the feeding of purin- or nuclein-containing substances to normal persons, to patients with chronic arthritis, and to patients with gout. In all of the tables exogenous uric acid will be expressed as the percentage of purin nitrogen in the substances fed which was excreted as uric acid nitrogen. In making the tabulations figures given by the observers quoted have been subjected to certain changes. In expressing the amounts of uric acid and of purin nitrogen, numerals beyond the second decimal place have been dropped. No decimals have been used in expressing the percentages of purin nitrogen excreted as uric acid nitrogen. We have supplied calculations wherever those requisite for our purposes had not been made by the author. Our additional calculations are designated in the tables by an asterisk. Observations have been collected only in which the experimental subjects received a known amount of some purin- or nuclein-containing substance while on an otherwise purin-free diet. The findings for normal man are given in Table 5.

Summary of Table 5. In normal human beings after feeding hypoxanthin the percentage of purin nitrogen excreted as uric acid nitrogen varied from 21 per cent. to 72 per cent.; after feeding a nucleinate or nucleic acid, from 22 per cent. to 52 per cent.; after giving adenin it was 41 per cent.; after feeding thymus it varied from 11 per cent. to 38 per cent., and after beef, ham or veal, from 8 per cent. to 74 per cent. The mean average percentage of excretion of exogenous uric acid nitrogen after feeding the above-named substances to normal individuals was 39 per cent., the extremes of excretion being 8 per cent. and 74 per cent. After feeding beef the exogenous uric acid varied from 8 per cent. to 44 per cent. in a person reported by Kaufmann and Mohr.[44] After administering hypoxanthin to a person reported by Ackroyd[34] the excretion of exogenous uric acid nitrogen was 21 per cent. after the first feeding and 65 per cent. after the second. Thus there is a considerable variation in the amount of exogenous uric acid both among different persons and in the same person. The time required to complete the excretion of the exogenous uric acid varied from one to five days.

TABLE 5.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY NORMAL MAN ON A PURIN-FREE DIET

Observer.	Observation period	Daily average endogenous output of uric acid in Gm.	Output of exogenous uric acid in Gm.	Per cent. of purin nitrogen excreted as uric acid N	Number of days of exogenous uric acid excretion.	Substance given.	Purin nitrogen in substance given†
Minkowski[32] .	18	0.23	1.82*	49*	3*	3 gm. hypoxanthin in 1 day	1.24*
Krüger and Smith[33]	1	0.46	2.31	62	3	3 gm. hypoxanthin in 2 days	1.24
Ackroyd[34] . .	1a	0.46	0.19	21	·2	0.75 gm. hypoxanthin in 1 day	0.31
	1b	0.46	0.60	65	4	0.75 gm. hypoxanthin in 1 day	0.31
	2	0.42	0.66	72	2	0.75 gm. hypoxanthin in 1 day	0.31
	3	0.35	0.36	39	3	0.75 gm. hypoxanthin in 1 day	0.31
Brugsch and Schittenhelm[29]	10	0.24	1.28	23	2	Sodium thymonucleinate 30 gm. in 3 days	1.86
	12	0.38	1.54	24	1	Sodium nucleinate from yeast, 30 gm. in 3 days	2.17
Pollak[35] . .	1	0.43	0.56	30	2	Sodium nucleinate 20 gm. in 1 day	0.79*
	2	0.42	0.45	38	2	10 gm. in 1 day	0.40*
	3	0.27	0.51	22	3	20 gm. in 1 day	0.79*
Mendel and Lyman[36]	W.W.H.	0.37	0.74	64	3	1.5 gm. hypoxanthin nitrate	0.39
	J.F.L.	0.38	0.66	57	3	1.5 gm. hypoxanthin nitrate	0.39
Plimmer, Dick, and Lieb[37]	..	0.43	0.12	..	1	13 gm. nucleic acid in 3 days	
Bloch[38] . .	1	0.49	0.94	48	2	10 gm. nucleic acid in 1 day	0.66
	2	0.50	0.83	42	3	10 gm. nucleic acid in 1 day	0.66
	3	0.33	1.03	52	2	10 gm. nucleic acid in 1 day	0.66
Mallory[39] . .	1	0.42	0.31	39	3	4 gm. nucleic acid in 1 day	0.26

* This figure represents our calculation made from the table given by the author quoted.
† The method of administration was per os in each instance.

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[34] Ackroyd, H.: Observations on Purin Metabolism. Bull. Com. for Study of Special Diseases, Edinburgh, 1907, 2, 146.

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[36] Mendel, L. B., and Lyman, J. E.: A Metabolism of Some Purin Compounds in the Rabbit, Dog, Pig, and Man. Jour. Biol. Chem., 1910–1911, 8, 115.

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[38] Bloch, B.: Beiträge zur Kenntniss des Purinstoffwechsels beim Menschen. Deutsch. Arch. f. klin. Med., 1905, 83, 499.

[39] Mallory, W. J.: Observations on Uric Acid Excretion in Gout and Rheumatoid Arthritis. Bull. Com. for Study of Special Diseases, 1908–1909, 3, 17.

TABLE 5.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY NORMAL MAN ON A PURIN-FREE DIET—(*Continued*)

Observer.	Observation period.	Daily average endogenous output of uric acid in Gm.	Output of exogenous uric acid in Gm.	Per cent. of purin nitrogen excreted as uric acid N.	Number of days of exogenous uric acid excretion.	Substance given.	Purin nitrogen in substance given†.
Morris[40] . .	1	0.38	0.17	22	2	4 gm. nucleic acid in 1 day	0.26
Krüger and Smith[33]	1a	0.46	0.15	41	2	0.3 gm. adenin in 1 day	
	1b	0.46	0.31	41	3	0.6 gm. adenin in 1 day	
Hirschstein[41] .	4	0.36*	1.45*	11*	1	1000 gm. thymus in 2 days	4.50*
Burian and Schur[42]	10	0.52	1.77	26	2	620 gm. thymus in 2 days	2.48
Ljungdahl[43] .	1	....	1.01	28	4	300 gm. thymus in 1 day	1.20
	2	....	1.37	38	5	300 gm. thymus in 1 day	1.20
	3	....	0.45	13	2	300 gm. thymus in 1 day	1.20
	4	....	0.87	24	2	300 gm. thymus in 1 day	1.20
	5	....	0.93	26	3	300 gm. thymus in 1 day	1.20
	6	....	1.17	33	3	300 gm. thymus in 1 day	1.20
Burian and Schur[42] . .	10	0.52	0.95	53	3	500 gm. liver in 1 day	0.60
	13	0.55	0.24	44	1	300 gm. ham in 1 day	0.18
	3	0.56	1.34*	74*	1	1000 gm. beef in 4 days	0.60*
	5	0.39	0.52*	38*	1	760 gm. beef in 4 days	0.46*
Kaufmann and Mohr[44]	7	0.54*	2.71*	44*	2*	900 gm. veal in 4 days	0.54*
		0.54*	0.12*	8*	3*	900 gm. beef in 4 days	0.54*
	8	0.47*	0.53*	59*	2*	500 gm. beef in 3 days	0.30*
Plimmer, Dick and Lieb[37]	..	0.43*	2.77*	47*	3	3500 gm. beef in 7 days	1.95*
Weiss[45] . .	1	0.36	0.51	46	3	750 gm. beef in 2 days	0.38
		0.36	1.01	53	3	1250 gm. beef in 2 days	0.63
Walker Hall[46] .	14	0.43	0.21	29	1	400 gm. beef in 1 day	0.24

[40] Morris, E. H.: Observations on the Uric Acid Excretion in One Normal Person, and in Four Cases of Rheumatoid Arthritis. Bull. Com. for Study of Special Diseases, Edinburgh, 1910, 3, 57.

[41] Hirschstein, L.: Die Beziehungen des Glykokolls zur Harnsäure. Ztschr. f. exper. Pathol. u. Therap., 1907, 4, 118.

[42] Burian, R., and Schur, H.: Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel. Arch. f. d. gesamt. Physiol., 1900, 80, 241.

[43] Ljungdahl, M.: Ueber die Harnsäureausscheidung bei den chronischen nicht gichtischen Polyarthritiden und ihre Bedeutung für die Differentialdiagnose zwischen Gelenkerkrankungen gichtischer und nicht gichtischer Natur. Ztschr. f. klin. Med., 1913–1914, 79, 177.

[44] Kaufmann, M., and Mohr, L.: Beiträge zur Alloxurkörperfrage und zur Pathologie der Gicht. Deutsch. Arch. f. klin. Med., 1902, 74, 141 and 586.

[45] Weiss, P.: Beiträge zur Wertbestimmung der Ausscheidung der endogenen und exogenen Harnsäure bei Gicht und anderen Erkrankungen. Ztschr. f. klin. Med., 1908, 66, 131.

[46] Hall, I. W.: The Purin Bodies of Foodstuffs, Manchester, 1902, p. 64.

TABLE 6.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY PATIENTS WITH CHRONIC ARTHRITIS WHO WERE ON A PURIN-FREE DIET

Observer.	Observation period.	Daily average endogenous output of uric acid in Gm.	Output of exogenous uric acid in Gm.	Per cent. of purin nitrogen excreted as uric acid N.	Number of days of exogenous uric acid excretion.	Substance given.	Purin nitrogen in substance given†.
Kaufmann and Mohr[44]	44	0.43	2.47	8	5	2500 gm. thymus in 5 days	10.00
	45	0.47	2.33	13	3	1500 gm. thymus in 3 days	6.00*
Ackroyd[34] . .	4a	0.26	0.59	64	3	0.75 gm. hypoxanthin in 1 day	0.31
	4b	0.26	0.46	50	2	0.75 gm. hypoxanthin in 1 day	0.31
	5	0.33	0.44	49	3	0.75 gm. hypoxanthin in 1 day	0.31
	6	0.32	0.57	61	3	0.75 gm. hypoxanthin in 1 day	0.31
	7	0.35	0.40	43	2	0.75 gm. hypoxanthin in 1 day	0.31
	8	0.33	0.21	34	3	0.5 gm. hypoxanthin in 1 day	0.21
	9	0.32	0.92	99	6	0.75 gm. hypoxanthin in 1 day	0.31
	10	0.34	0.53	87	7	0.5 gm. hypoxanthin in 1 day	0.21
	11	0.53	0.61	100	7	0.5 gm. hypoxanthin in 1 day	0.21
	12	0.49	0.31	33	6	0.75 gm. hypoxanthin in 1 day	0.31
	14	0.34	0.41	44	9	0.75 gm. hypoxanthin in 1 day	0.31
Mallory[39] . .	1b	0.35	0.14	15	2	0.75 gm. hypoxanthin in 1 day	0.31
	2b	0.30	0.24	25	4	0.75 gm. hypoxanthin in 1 day	0.31
	c	0.30	0.33	35	3	0.75 gm. hypoxanthin in 1 day	0.31
	d	0.30	0.25	27	3	0.75 gm. hypoxanthin in 1 day	0.31
	3b	0.30	0.50	53	2	0.75 gm. hypoxanthin in 1 day	0.31
	5b	0.30	0.55	59	4	0.75 gm. hypoxanthin in 1 day	0.31
	6b	0.31	0.38	41	3	0.75 gm. hypoxanthin in 1 day	0.31
Morris[40] . .	2b	0.21	0.25	27	3	0.75 gm. hypoxanthin in 1 day	0.31
	3b	0.20	0.40	43	3	0.75 gm. hypoxanthin in 1 day	0.31
Mallory[39] . .	1a	0.35	0.06	7	3	4 gm. nucleic acid in 1 day	0.26
	2a	0.30	0.24	31	2	4 gm. nucleic acid in 1 day	0.26
	3a	0.30	0.26	32	2	4 gm. nucleic acid in 1 day	0.26
	4	0.39	0.36	46	3	4 gm. nucleic acid in 1 day	0.26
	5a	0.30	0.63	80	8	4 gm. nucleic acid in 1 day	0.26
	6a	0.31	0.76	97	6	4 gm. nucleic acid in 1 day	0.26
Morris[40] . .	2a	0.21	0.14	18	4	4 gm. nucleic acid in 1 day	0.26
	3a	0.20	0.14	18	3	4 gm. nucleic acid in 1 day	0.26
	4	0.31	0.81	103	7	4 gm. nucleic acid in 1 day	0.26

* This figure represents our calculation made from the table given by the author quoted.
†‡The method of administration was per os in each instance.

TABLE 6.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY PATIENTS WITH CHRONIC ARTHRITIS WHO WERE ON A PURIN-FREE DIET—(*Continued*)

Observer.	Observation period.	Daily average endogenous output of uric acid in Gm.	Output of exogenous uric acid in Gm.	Per cent. of purin nitrogen excreted as uric acid N.	Number of days of exogenous uric acid excretion.	Substance given.	Purin nitrogen in substance given.†
Ljungdahl[46]	1	....	0.95	26	2	300 gm. thymus	1.20
	2	....	0.54	15	2	300 gm. thymus	1.20
	3	....	0.39	11	2	300 gm. thymus	1.20
	4	....	0.46	19	2	200 gm. thymus	0.80
	5	....	0.69	19	2	300 gm. thymus	1.20
	6	....	1.15	48	7	200 gm. thymus	0.80
	7	....	1.20	33	7	300 gm. thymus	1.20
	8	....	0.50	14	2	300 gm. thymus	1.20
	9	....	0.95	26	5	300 gm. thymus	1.20
	10	....	0.28	8	1	300 gm. thymus	1.20
	11	....	0.24	7	1	300 gm. thymus	1.20
	12	....	1.12	31	6	300 gm. thymus	
Hösslin and Kato[47]	1	0.28*	1.41*	60*	5*	10 gm. sodium nucleinate	0.66*
	4	0.30*	0.12*	6*	2*	10 gm. sodium nucleinate	0.66*
	5	0.35*	2.30*	80*	5*	15 gm. sodium nucleinate	0.99*
	6	0.33*	0.70*	24*	3*	15 gm. sodium nucleinate	0.99*
	8	0.35*	0.14*	7*	1*	10 gm. sodium nucleinate	0.99*
	10	0.29*	0.20*	6*	1*	15 gm. sodium nucleinate	0.99*
	11	0.34*	0.02*	1*	1*	15 gm. sodium nucleinate	0.99*
	12	0.42*	0.89*	31*	4*	15 gm. sodium nucleinate	0.99*

Table 6, showing the output of exogenous uric acid after feeding purin- or nuclein-containing substances to patients with chronic non-gouty arthritis, is for the most part taken from one compiled by Mallory.[39] All patients were on a purin-free diet.

Summary of Table 6. In patients with chronic non-gouty arthritis the percentage of purin nitrogen excreted as uric acid nitrogen after feeding hypoxanthin ranged from 15 per cent. to 99 per cent., after giving nucleic acid from 77 per cent. to 103 per cent., after sodium nucleinate from 1 per cent. to 80 per cent., and after thymus from 8 per cent. to 48 per cent. The mean average excretion of all these substances was 38 per cent. After feeding hypoxanthin the exogenous uric acid excretion varied from 50 per cent. to 64 per cent. in 1 of the Ackroyd's[34] cases, and from 25 per cent. to 35 per cent.

[47] von Hösslin, H., and Kato, K.: Ueber Harnsäureausscheidung bei Gicht und Gelenkrheumatismus. Deutsch. Arch. f. klin. Med., 1910, 99, 301.

in 1 reported by Mallory.[39] The table shows that there is great variation in the amount of exogenous uric acid excreted by the different patients. This was also found in normal persons (Table 5). The time required to excrete the exogenous uric acid varied from one to nine days.

The cases reported by Kaufmann and Mohr,[44] Ackroyd,[34] Mallory[39] and Morris[40] were without evidences of nephritis. It is inferred from the text in the reports of Ljungdahl[43] and of Hösslin and Kato[47] that the patients were not nephritics.

We have studied the excretion of uric acid after a meal of sweetbreads in a patient with chronic polyarthritis. There were no evidences of kidney disease or of gout in this patient. The findings are given in Table 7.

TABLE 7.—EXOGENOUS URIC ACID EXCRETION IN CHRONIC ARTHRITIS

(W. H. K., Med. No. 5278. Diagnosis: Chronic arthritis. For notes on this patient see Case 5.)

Date.	Time of collection.	Urine.		Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Non-protein N in Mg. per 100 c.c.	Uric acid in Mg. per 100 c.c.	
Oct. 31	.....	.....	.....	.....	.....	Purin-free diet begun.
Nov. 9	.....	.....	.....	27.9	1.5	
16 to 17	7 A.M. to 7 A.M.	1480	0.44			
17 to 18	.....	1010	0.39			
18 to 19	.....	845	0.38			
19 to 20	.....	1235	0.37			
20 to 21	.....	1310	0.43			
21	1 P.M.	....	.....	.....	.....	Patient given 184 Gm. sweetbreads.
	7 P.M.	.....	.....	.....	2.6	
21 to 22	1 P.M. to 1 P.M.	7429	0.93			
22	11 A.M.	.....	.....	.....	1.5	
22 to 23	1 P.M. to 1 P.M.	1490	0.53			
23 to 24	1 P.M. to 1 P.M.	925	0.49			
24 to 25	1 P.M. to 1 P.M.	905	0.33			

Endogenous output of uric acid November 17 to 21 = 2.01 gm.

Endogenous output of uric acid per day = 0.4 gm.

Exogenous output of uric acid November 22 to 24 = 0.75 gm.

Purin nitrogen in 184 gm. of sweetbreads calculated according to Burian and Schur = 0.83 gm.

Per cent. of purin nitrogen excreted = 30 per cent.

Uric acid determinations made by the uric acid reagent method.

TABLE 8.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY GOUTY PERSONS ON A PURIN-FREE DIET

Observer.	Observation period.	Daily average endogenous output of uric acid in Gm.	Output of exogenous uric acid in Gm.	Per cent. of purin nitrogen excreted as uric acid N.	Number of days of exogenous uric acid excretion.	Substance given.	Purin nitrogen in substance given.†
Brugsch and Schittenhelm[29]	4	0.23	0.39	14	4	Sodium thymonucleinate, 20 gm. in 2 days	1.24
	5	0.33	0.57	15	5	Sodium thymonucleinate, 20 gm. in 2 days	1.24
	11	0.13	0.35	6	6	Sodium thymonucleinate, 30 gm. in 3 days	1.86
See footnote[49]	8	0.25	0.16	16	3	Sodium thymonucleinate, 5 gm. in 1 day	0.31
See footnote[29]	4	0.22	0.44	20	4	Yeast sodium nucleinate, 10 gm. in 1 day	0.72
		0.23	0.44	20	4	Yeast sodium nucleinate, 50 gm. in 5 days	3.61
	5	....	0.00	0	0	Yeast sodium nucleinate, 20 gm. in 2 days	1.44
	13	0.31	1.54	36	5	Yeast sodium nucleinate, 20 gm. in 2 days	1.44
Neustadt[48]	K2	0.48	0.00	0	..	8 gm. thymonucleic acid in 1 day	
Pollak[35]	4	0.06	0.19	16	4	10 gm. nucleic acid in 1 day	0.40
	5	0.23	0.24	19	2	10 gm. nucleic acid in 1 day	0.40
	6	0.27	0.43	20	3	18 gm. nucleic acid in 1 day	0.71
Mallory[39]	9a	0.18	0.02	3	1	4 gm. nucleic acid in 1 day	0.26
	10a	0.31	0.02	3	1	4 gm. nucleic acid in 1 day	0.26
	11a	0.17	0.24	30	4	4 gm. nucleic acid in 1 day	0.26
Brugsch and Schittenhelm[49]	1	0.29	0.16	13	2	1 gm. hypoxanthin in 1 day	0.41
	2	0.29	0.15	12	1	1 gm. hypoxanthin in 1 day	0.41
Mallory[39]	9b	0.18	0.03	3	1	0.75 gm. hypoxanthin in 1 day	0.31
	10b	0.31	0.09	10	2	0.75 gm. hypoxanthin in 1 day	0.31
	11b	0.17	0.10	10	3	0.75 gm. hypoxanthin in 1 day	0.31
Rotky[50]	3–2	0.34	0.07	11	3	0.5 gm. hypoxanthin in 1 day	0.21
Neustadt[48]	1.2	0.36	0.79	109	4	0.5 gm. hypoxanthin in 1 day	0.21
	K3	0.48	0.02	5	3	0.25 gm. hypoxanthin in 1 day	0.10

* This figure represents our calculation made from the table given by the author quoted.
† The method of administration was per os in each instance.

[48] Neustadt, G.: Das Verhalten verfütterter Purinbasen bei der Gicht. Ztschr. f. exper. Path. u. Therap., 1911–1912, 10, 296.

[49] Brugsch, T., and Schittenhelm, A.: Zur Stoffwechselpathologie der Gicht. VIII Mittheil. Ztschr. f. exper. Path. u. Therap., 1908, 1909, 5, 215.

[50] Rotky, H.: Beiträge zur Pathologie des Nukleinstoffwechsels. Deutsch. Arch. f. klin. Med., 1909–1910, 98, 540.

TABLE 8.—SUMMARY OF PREVIOUS OBSERVATIONS ON EXOGENOUS URIC ACID EXCRETION BY GOUTY PERSONS ON A PURIN-FREE DIET—(*Continued*)

Observer.	Observation period.	Daily average endogenous output of uric acid in Gm.	Output of exogenous uric acid in Gm.	Per cent. of purin nitrogen excreted as uric acid N.	Number of days of exogenous uric acid excretion.	Substance given.	Purin nitrogen in substance given.†
		0.45	0.38	61	3	0.5 gm. hypoxanthin in 1 day	0.21
		0.48	0.09	15	3	0.5 gm. hypoxanthin in 1 day	0.21
		0.51	0.42	69	4	0.5 gm. hypoxanthin in 1 day	0.21
Levine and Kristeller[51]	1	0.24	0.15	20	4	7.5 gm. uric acid in 1 day	2.50
		0.24	0.00	0	0	7.5 gm. uric acid in 1 day	2.50
	2	0.23	1.14	5	6	24 gm. uric acid in 4 days	8.00
		0.23	0.86	2	2	24 gm. uric acid in 4 days	8.00
	1	0.23	0.23	3	4	Nucleic acid, 1 day	2.83
	2	0.23	1.50	6	4	Nucleic acid, days	48.0
Neustadt[48]	1.6	0.41	0.21	38	3	0.35 gm. adenin in 1 day	0.18
Brugsch and Schittenhelm[49]	..	0.25	0.44	41	5	0.7 gm. adenin in 1 day	0.36
Kaufmann and Mohr[44]	39	0.46*	2.31*	22*	4*	800 gm. thymus in 4 days	3.60*
	40	0.50*	1.44*	12*	2*	900 gm. thymus in 2 days	4.05*
	41	0.49*	1.30*	8*	2*	1200 gm. thymus in 4 days	5.40*
	42	0.40*	0.72*	5*	1*	900 gm. thymus in 3 days	4.05*
	46	0.32*	2.69*	22*	5+*	900 gm. thymus in 3 days	4.05*
Strauss[52]	..	0.41*	0.33*	8*	2	325 gm. thymus in 1 day	1.46*
Brugsch[53]	1	0.55*	0.00*	0*	0*	800 gm. thymus in 4 days	3.00*
Hirschstein[41]	5	0.06*	17.00*	9*	0+*	1000 gm. thymus in 2 days	4.50*
Rotky[24]	3	0.34*	0.04	3	2	100 gm. thymus in 1 day	0.45*
Kaufmann and Mohr[44]	47	0.39	0.40	27*	1	800 gm. veal in 4 days	0.48*
		0.40	0.30	21*	1	800 gm. beef in 4 days	0.48*
Soetbeer[54]	3	0.42	0.12	25*	1+*	250 gm. beef in 1 day	0.15*
	4	0.50	0.08	10*	2+*	500 gm. beef in 1 day	0.30*
	5	0.30*	0.00*	0*	..	700 gm. beef in 2 days	0.18*
Brugsch[53]	..	0.55	0.00	0	..	800 gm. beef in 8 days	0.48*
Soetbeer[54]	2	0.28	0.92	57	3+*	900 gm. ham in 3 days	0.54*
Weiss[45]	..	0.29	0.42	37	8	750 gm. beef	0.38
Hall[55]	4	0.17*	0.22*	106	3	Beef extract	0.07

[51] Levene, P. A., and Kristeller, L.: Nitrogen and Nuclein Metabolism in Gout. Jour. exper. Med., 1912, 16, 303.

[52] Strauss, H.: Pathogenese und Therapie der Gicht. Würzburger Abhandl. a. d. Gesamt. d. prakt. Med., 1902, 2, 209.

[53] Brugsch, T.: Zur Stoffwechselpathologie der Gicht. Ztschr. f. exper. Path. u. Therap., 1905–1906, 2, 619.

[54] Soetbeer, F.: Ueber den Einfluss der Nährungsaufnahme auf die Ausscheidung der Harnsäure bei Arthritis urica. Ztschr. f. physiol. Chem., 1903–1904, 40, 25.

[55] Hall, I. W.: The Chemical Pathology of Gout. Brit. Med. Jour., 1904, 2, 744.

Thirty per cent. of the purin nitrogen fed was excreted as uric acid nitrogen by our patient. These findings are comparable to those reported in the literature.

The exogenous uric acid excretion by gouty persons who were under the same experimental conditions as the normal and arthritic subjects in the foregoing tables is given in Table 8.

Summary of Table 8. In gouty patients the percentage of purin base nitrogen excreted as uric acid nitrogen after feeding hypoxanthin varied from 5 per cent. to 109 per cent., after adenin it was 40 per cent., after giving nucleic acid it ranged from 3 per cent. to 30 per cent., after sodium nucleinate from none to 36 per cent., after thymus from none to 22 per cent., and after some form of beef or ham from none to 106 per cent. The mean average percentage of excretion as exogenous acid nitrogen of all these substances fed was 20 per cent.

TABLE 9.—EXOGENOUS URIC ACID EXCRETION IN GOUT

(A. L. E., Med. No. 5297. Diagnosis: Gout.)

Date.	Time of collection.	Urine.		Blood.		Remarks.
		Amount in c.c.	Uric acid in Gm.	Non-protein N in Mg. per 100 c.c.	Uric acid in Mg. per 100 c.c.	
1916						
Nov. 1	.....	.....	.....	.....	.....	Purin-free diet begun.
20 to 21	7 A.M. to 7 A.M.	475	0.15			
21 to 22	.....	Lost				
22 to 23	7 A.M. to 7 A.M.	695	0.14			
23 to 24	7 A.M. to 7 A.M.	460	0.10			
24 to 25	7 A.M. to 7 A.M.	715	0.13			
25	1 P.M.	.....	.....	54.3	4.5	
	1 P.M.	.....	.....	.....	.....	Patient given 150 gm. sweetbreads.
	7 P.M.	.....	.....	.....	5.3	
25 to 26	1 P.M. to 1 P.M.	725	0.19			
26	1 P.M.	.....	.....	.....	5.1	
26 to 27	1 P.M. to 1 P.M.	895	0.19			
27 to 28	1 P.M. to 1 P.M.	735	0.13			
29	1 P.M.	.....	.....	.....	4.8	

Endogenous output of uric acid November 21 to 25 = 0.52 gm.

Endogenous output of uric acid per day = 0.13 gm.

Exogenous output of uric acid November 26 to 27 = 0.12 gm.

Purin nitrogen in 150 gm. of sweetbreads calculated according to Burian and Schur = 0.68 gm.

Per cent. of exogenous purin nitrogen excreted = 6.

Uric acid determinations made by the uric acid reagent method.

It will be noted that the exogenous uric acid output in the patients whose urine contained albumin and casts was as great as in those in whom the urine was reported as normal.

TABLE 10.—EXOGENOUS URIC ACID EXCRETION IN GOUT AFTER FEEDING SWEETBREADS

J. J. N. White, male, aged 35. Many tophi on hands and feet. Diagnosis: Gout.

Date.	Time of collection.	Urine.		Blood, uric acid in Mg. per 100 c.c.	Remarks.
		Amount in c.c.	Uric acid in Gm.		
1916					
Oct. 7	.....	.....	.....	.....	Purin-free diet begun.
12 to 13	7 A.M. to 7 A.M.	1690	0.26		
13 to 14	7 A.M. to 7 A.M.	1440	0.25		
14 to 15	7 A.M. to 7 A.M.	1570	0.27		
15 to 16	7 A.M. to 7 A.M.	1860	0.26		
16 to 17	7 A.M. to 7 A.M.	2100	0.33		
17 to 18	7 A.M. to 7 A.M.	1860	0.25		
18 to 19	7 A.M. to 7 A.M.	1770	0.25		
19 to 20	7 A.M. to 7 A.M.	1515	0.40		
20	12 noon	.....	.....	2.2	188 gm. of thymus.
20 to 21	7 A.M. to 7 A.M.	1620	0.49	4.4	Acute attack of gout.
21 to 22	7 A.M. to 7 A.M.	2100	0.59	8.7	
22 to 23	7 A.M. to 7 A.M.	1500	0.29	2.7	
23 to 24	7 A.M. to 7 A.M.	1865	0.37		
24 to 25	7 A.M. to 7 A.M.	1660	0.25	5.0	
Nov. 7	.....	.....	.....	7.4	

Endogenous output of uric acid October 13 to 19 = 1.87 gm.

Endogenous output of uric acid per day = 0.27 gm.

Exogenous uric acid excreted October 21 to 22 = 0.67 gm.

Purin nitrogen in 188 gm. of sweetbreads according to Burian and Schur = 0.9 gm.

Percentage of purin nitrogen excreted as uric acid nitrogen = 24.

We have studied the uric acid excretion in 2 cases of gout after feeding sweetbreads. The findings are given in Tables 9 and 10. The patient whose data are given in Table 8 has already been described as Case 9. The patient whose data appears in Table 9 was one who used alcoholic drinks to excess. During the previous nine years the patient had had six attacks of podagra in the right great toe-joint. In the previous six years there had been several polyarticular attacks of arthritis, gouty in nature, which involved the joints of the hands, knees, toes and ankles. During the study

of the patient's uric acid excretion an attack of gout occurred the day following the ingestion of 188 gm. of sweetbreads. The middle finger, dorsum of the hand and wrist were involved. On physical examination large tophi were found in the left ear, about the olecranon processes of both ulnæ and on the plantar surfaces of both wrists, and on all the fingers. Sodium urate crystals were obtained from certain of the tophi. There were no evidences of cardiovascular disease. The blood-pressure was 126 mm. systolic and 96 mm. diastolic. The urine contained neither albumin nor casts. The patient was put on a purin-free diet October 8, 1916.

Our patients with gout excreted 6 per cent. and 24 per cent. of the purin nitrogen contained in the sweetbreads in the form of uric acid nitrogen. These findings are comparable to those reported for gout cases in the literature.

The results obtained by a comparative study of exogenous uric acid excretion by normal, by arthritic, and by gouty persons are shown in Tables 11 and 12.

TABLE 11.—PERCENTAGE OF PURIN NITROGEN EXCRETED AS URIC ACID NITROGEN AFTER FEEDING PURIN- OR NUCLEIN-CONTAINING SUBSTANCES

Diagnosis.	Number of cases.	Total number of experiments.	Number of experiments and percentages of purin nitrogen excreted as uric acid nitrogen.			
			0–10	10–20	20–30	30–100
Normal	35	4	1	2	11	26
Chronic arthritis . .	41	52	8	9	7	28
Gout	32	50	19	13	7	11

Table 11 shows conclusively that the output of exogenous uric acid is usually smaller in gout than in either normal or arthritic persons.

Twenty-eight, or 87.9 per cent., of the gouty patients excreted as uric acid nitrogen less than 20 per cent. of the purin nitrogen while thirty-one, or 88.6 per cent., of normal persons and twenty-five, ingested, or 69.7 per cent., of non-gouty, arthritic patients excreted

more than 20 per cent. Regardless of the substances fed the average exogenous uric acid nitrogen excretion in gout was 20 per cent., while by the normal persons it was 39 per cent., and by arthritic patients 38 per cent. The small output of exogenous uric acid occurs frequently enough in gout to be considered as a symptom of that disease. But as a pathognomonic symptom of gout it is not of much importance, since it also occurs in 11.4 per cent. of normal persons, and in 30.3 per cent. of arthritic non-gouty patients.

A prolonged excretion of exogenous uric acid has been considered as a symptom of gout. The duration in days of the output of exogenous uric acid has been compiled from Tables 5 to 10 and the results are given in Table 12.

TABLE 12.—DURATION IN DAYS OF EXOGENOUS URIC ACID EXCRETION AFTER FEEDING PURIN- OR NUCLEIN-CONTAINING SUBSTANCES

Diagnosis.	Number of cases.	Total number of experiments.	Number of experiments, with duration in days, of exogenous uric acid excretion.								
			1	2	3	4	5	6	7	8	9
Normal . . .	35	40	6	15	16	2	1				
Chronic arthritis	41	52	5	13	15	4	4	4	5	1	1
Gout	32	46	9	10	11	7	4	2	1	2	

All normal persons excreted the exogenous uric acid within five days. Of fifty-two experiments on arthritic patients, the exogenous uric acid output was completed within five days in forty-one, or 78.8 per cent., and of forty-six experiments on the gouty persons the output was completed within five days in forty-one, or 89.1 per cent. Therefore, a prolongation of the excretion of exogenous uric acid over that of the normal does not occur frequently enough in gout to be considered a symptom of that disease.

The striking fact brought out in the last two tables is the great variations in the percentage output of exogenous uric acid and in its duration. Either a delayed and diminished output is not evidence of disturbances in the intermediary metabolism of nucleins, or the intermediary metabolism of nucleins is easily deranged.

Summary and Discussion. Our studies on the intravenous injection of uric acid and the feeding of nuclein-containing material, together with the compilations we have made from reports in the literature, show that in normal and non-gouty as well as in gouty persons there is great variability in the quantity and in the duration of exogenous uric acid excretion. For this reason a diminished or a protracted exogenous uric acid output most probably results from factors other than disturbances in the nuclein intermediary metabolism. If this is not true, then derangements in nuclein metabolism are so common that their importance in the etiology of any diseased condition is problematic.

Umber[56] advanced the hypothesis that the failure of gouty persons to excrete exogenous uric acid was due to a special affinity of the tissues for uric acid. We have found that intravenously injected uric acid usually remains in the blood stream longer in gouty than in non-gouty persons. The reverse would have been expected if Umber's theory were correct.

By statistical evidence we have shown that in the majority of gouty persons the uric acid in the blood is more than 3 mg. per 100 c.c. when determined by the method of Folin and Denis. That the substance which has been determined was actually uric acid is made probable by the following considerations: (1) It is well known that in gout there is a deficient output of uric acid; this substance would then tend to accumulate in the blood; (2) less uric acid is found in the blood of persons without gout than of those with that disease. The conditions which form exceptions to this statement have already been enumerated, but their character is such that in the large majority retention of uric acid is readily explained; (3) following the intravenous injections of uric acid an increase in that substance occurs in the blood.

The fate of that part of intravenously injected uric acid which is not excreted within the first few days is unknown. In fact, this additional uric acid disappeared from the blood in all of our cases, except one, before its excretion began. Since uric acid is not known to be destroyed in the body, we offer the explanation that the excess

[56] Umber, F.: Ernährung und Stoffwechselkrankheiten. Ed. 2, Berlin, 1914.

which we injected went into the body tissues. Van Slyke[57] has shown that intravenously introduced amino-acids quickly disappear from the blood. He discovered that they were to be found in the muscles, where they were held either mechanically or in loose molecular combinations. Urea[58] behaves in the same manner. That the intravenously injected uric acid does not enter into some combinations in the blood which prevents its determination by the Folin and Denis method is indicated by the ability to recover all uric acid which is added to blood *in vitro*.

From our studies and those of others it appears that more than 3 mg. per 100 c.c. of blood is a symptom of gout. But whether or not retention of uric acid after its intravenous injection, or after feeding substances containing purin or nucleins, is to be regarded as evidence of gout is open to question, since we have shown that the failure to eliminate exogenous uric acid is not peculiar to gout.

We are impressed with the importance of carrying out studies on uric acid elimination on persons who are really normal. It may be doubted whether some of the so-called normal subjects used for physiologic studies on uric acid elimination were not pathologic. Before considering an experimental subject as normal it is necessary that a thorough medical examination be made and that the modern laboratory tests, especially those for renal function, be employed.

Conclusions.—1. More than 3 mg. of uric acid per 100 c.c. of blood, with the patient on a purin-free diet, is a symptom of gout, but it is not diagnostic of this disease.

2. No relation exists between the amount of uric acid and of total non-protein nitrogen found in the blood of gouty persons.

3. A marked retention of non-protein nitrogen is not frequent in gout.

4. The excretion of exogenous uric acid by normal, by arthritic, and by gouty persons varies greatly both in amount and in duration.

5. The retention of exogenous uric acid is a symptom of questionable importance in the diagnosis of gout.

[57] Van Slyke, D. D.: The Fate of Protein Digestion Products in the Body. III. The Absorption of Amino-Acids from the Blood and Tissues. Jour. Biol. Chem., 1914, 16, 197.

[58] Marshall and Davis: Urea: Its Distribution and Elimination from the Body. Jour. Biol. Chem., 1914, 18, 53.

We wish to thank Dr. Christian for allowing us to study the gouty patients in his wards. We are much indebted to Dr. Otto Folin for advice in the interpretation of certain findings. The 3 cases of insanity were studied at the Boston Psychopathic Hospital through the courtesy of Dr. E. E. Southard. One of the cases of gout was studied at the Massachusetts General Hospital through the coöperation of the orthopedic department.

DISCUSSION

Dr. Christian wished to emphasize the very great importance of a very healthy atmosphere of skepticism that should exist around any investigation of the uric acid metabolism in gout. Dr. Pratt and Dr. McClure are, themselves, pretty good skeptics on this subject; and a great part of the cases of gout were investigated in (the speaker's) wards at the Brigham Hospital in the light of the further skepticism he and his associates supplied. His reason for saying that was that he was perfectly sure that in a great many of the previous studies on gout the cases may not have been cases of gout. As a result of the Brigham Hospital studies on gout he would draw the conclusion that the only safe case to advance, from the point of view of metabolism studies, as a case of gout, is the patient in whom you can demonstrate definitely the deposit of uric acid, either in the form of tophi that you can palpate, or from which you can secure the uric acid crystals, or in the form of depositions in the bone which you can demonstrate with the *x*-rays.

By that he did not mean that cases which did not show these things are not gout; but if they do show them, we can book them as assuredly gout, and report them, as metabolism studies upon cases of gout. If one looks over the literature, it is certain that some patients reported as gout are very probably non-gouty cases. Dr. Pratt's cases are cases of gout in whom urate deposits have been demonstrated. Dr. Christian wished to emphasize his belief that unless you find those deposits at the present time, however thoroughly you studied the metabolism, you cannot be sure the patient has gout.

The *x*-ray pictures of the joints, in all the Brigham cases save one, were pictures of a simple polyarthritis of the infectious type; and they had only one case that showed in the *x*-ray characteristics of gout. It was, in that connection, interesting to note that we very frequently get from our *x*-ray friends the diagnosis, based on their examination, of gout in patients who

most assuredly have not gout, where the bony changes, to those who are familiar with gout patients, are most assuredly not those of gout; but simply polyarthritis with certain changes in the bone, certain forms of atrophy, frequently misinterpreted by the roentgenologist as gouty changes though they are not gout at all.

Dr. Barker said that if these cases reported by Dr. Pratt and Dr. McClure were instances of true gout, the observations are very important, for they run contrary to the generally accepted opinion regarding content of the urine of the blood endogenous uric acid in this disease.

He could corroborate the statements of both speakers regarding the difficulty of diagnosis of true gout in the absence of tophi, or in the absence of the typical *x*-ray pictures of the affected joints. The majority of cases diagnosed at watering places as gout are not gouty cases at all, but are cases either of infectious arthritis, or of hypertrophic osteoarthritis. The criteria for the diagnosis of gout, aside from tophi and *x*-ray findings, are very unsatisfactory: even the appearance of acute inflammation, in the night, in the great toe-joint, is not necessarily in the speaker's opinion, a safe criterion for the diagnosis of gout. Then, again, the unreliability of the methods for studying uric acid must be emphasized. The methods that we have, as yet, are very faulty. Even Foliu, whose very simple method was used, feels that his own method is not as satisfactory as he would like it to be. Dr. Barker thought the evidence strongly favors the view that in gout there is a renal insufficiency as regards the excretion of uric acid, even in the absence of other signs of renal insufficiency. As had more than once been brought out in this meeting, the elective disturbances of renal excretion are becoming very important; and it seemed to him quite probable that in gout we have to deal, in the early part of the disease, with an elective disturbance, involving the excretion of uric acid in the urine. As to disturbances of the intermediary metabolism of nucleins and other sources of uric acid there appeared, in his opinion, very little if any evidence in favor of their existence. In at least one case of true gout that came to autopsy, Jones and Miller tested the organs for all the ferments that are concerned in the degradation of nucleic acid, the nucleotides, the nucleosides and the purin bases, and all those ferments were present, apparently in normal distribution, in the tissues in that particular autopsy. There is, it must be remembered, no evidence—at least no satisfactory evidence—of the existence of a uric acid-destroying ferment in the human blood, though such a ferment undoubtedly exists in the tissues of some animals. This urease, postulated by the German observers for human tissues also, has not been found in the human body in this country by Walter Jones and his colleagues, despite careful search for it, and the speaker considered it very doubtful if it exists; so that the best-supported view of the pathogenesis of gout would seem to be that which views the disturbances as due

to faulty elimination of uric acid by the kidney and its retention within the body in excess.

What it is that precipitates an acute attack of gout in the night has been, and continues to be an interesting and unanswered question. He would not be surprised if toxic or infectious factors, sometimes at any rate, play a role in the precipitation of the acute attack; and in the acute attack it would appear that something brings about a sudden solution of uric acid in a place where it has been deposited; this solution is extremely irritating and quickly arouses an acute local inflammation.

Dr. Jacobi said he knew quite well that the diagnosis of gout had been made when a large quantity of uric acid was found in the urine: this was one way in which gout was diagnosticated. Another way whereby it was diagnosticated during his own time (and that is not so very long ago) was when there was no uric acid in the urine. When there was uric acid it proved gout, and when there was no uric acid in the urine it also proved gout; because it was concealed, because it did not come to the surface. That is not a joke. He had read that in a number of articles out of the books; so next year he thought we should find one or two more papers on gout and its diagnosis.

Dr. Pratt (closing) endorsed the statements of the three speakers. It is generally held that if a gouty patient is on a purin-free diet the output of uric acid will be so low as to be of diagnostic value. Our gouty patients, however, excreted as much uric acid on a purin-free diet as did the non-gouty. Hence no importance, diagnostically, could be attached to the output of endogenous uric acid in these cases of gout.

Careful studies of the uric acid metabolism should be made during non-gouty febrile states, especially during attacks of acute rheumatic fever. These would serve as controls to the observations made in gout. In this way further light might be thrown on the disturbance of nuclein metabolism that is thought to be the underlying cause of the disease. It is important to study the renal function in young individuals during or subsequent to attacks of podagra. If studies are confined to cases of gout which exhibit tophi, then the disturbance in renal function may well be secondary to the gout, as tophi rarely appear earlier than eight to ten years after the first attack of acute gout.

If the retention of uric acid in the body is due to damaged kidneys, then disturbances in the renal function could probably be demonstrated as soon as the first attack of podagra develops. Unfortunately no studies have been made by modern methods of the renal function early in the disease.

STUDIES OF DIGESTION

I. Effect of Stimuli from the Lower Bowel on the Rate of Emptying the Stomach.
II. Some Effects of Massage on the Colon.

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I. Effect of Stimuli from the Lower Bowel on the Rate of Emptying the Stomach. It has been shown by Cannon and others that irritation of the colon may delay the emptying of the stomach. This is striking and well known when powerful stimuli occur as in intestinal injury, in cutting, drying or handling the bowel. Here there is a definite protective mechanism holding back food above until some measure of healing occurs below.

Some men have also emphasized the effect of distention or irritation of the lower bowel by enemata, stasis in the ileum, inflammation of the appendix, adhesions in the ileocecal region, etc., in causing the stomach to empty slowly. (Hirsch,[1] Alvarez,[2] Baumstark,[3] Jordan,[4] Eisen,[5] Smithies,[6] Barclay,[7] Cole,[8] Ochsner,[9] Borbjarg.[10]) We have studied a group of such cases to find out how frequently this occurs and what sort of irritation gives this result. We have a series of clinical observations, and also of animal experiments.

Our results all point definitely the same way. First, regarding *frequency*—delay in emptying the stomach, is the exception, not the rule, in lesions of the lower bowel. Second, regarding the *kind of irritation*, a strong stimulus is needed from the lower bowel to slow the stomach.

Technic of Observations. We judged the time of emptying the stomach by watching the progress of a barium meal with the

roentgen rays and fluorescent screen in men and cats. A carbohydrate meal was chosen because it favors prompt emptying of the stomach; we used potato gruel, mixed with barium sulphate, in the proportion of 100 grams of barium to 500 c.c. of gruel. We gave a 500 c.c. meal to the men and 25 c.c. to the cats, and studied the residues in the stomach after five or six hours in men and after two or three hours in cats.

We tried to avoid other factors causing delay in emptying the stomach, such as emotion, trauma, etc. For example, we might expect that fastening a cat to a holder, giving a meal by stomach-tube, and then a rectal injection, would produce such unpleasant emotions that observation on the time of emptying the stomach would have little value. We used elderly female cats and found that with a little practice these things could be deftly done within a few minutes, and the psychology of these cats is such that, if kindly treated, they were purring and contented within a minute or two after release from the holder. For later *x*-ray examinations no holder was needed.

Operative trauma and the use of a fistula or injections through the peritoneum into the bowel were avoided by simply passing a catheter per rectum through the colon up to the cecum and making injections through this; with the colon empty, and a catheter of proper size and flexibility (16 French), this is easily done under the fluorescent screen. Irritants to be injected were usually mixed with a little barium sulphate and the injection also made under the fluorescent screen to control how much was given and exactly where the injection was placed.

The Effect of Mechanical Filling or Distention of the Colon. The men were given by mouth 500 c.c. of barium potato gruel. The cats were fed by stomach-tube with 25 c.c. of the gruel. The cats were released at once and were not examined for two or three hours. In men, bland rectal injections of 1000 to 1500 c.c. of potato gruel were given and retained as long as possible, usually from one to one and one-half hours. In cats a similar injection of 30 to 40 c.c. was used.

This had little or no effect upon the emptying of the stomach. Food passed steadily through the pylorus while the enema was

retained and the stomach was entirely empty within the normal period in each of the 10 cases in which this was tried. The only effect was a slight delay in the action of the stomach for the first few minutes. This does not agree with the statement of Alvarez that introduction of food at the lower end of the digestive tract markedly retards the progress of material coming down from above.

The fact that patients occasionally vomit after rectal feeding is poor evidence of reflex action from the colon to the stomach, because rectal feeding is usually given on account of *previous* vomiting in gastric ulcer, stenosis, etc., and the fact remains that most patients do *not* vomit after rectal feeding.

The Effect of Stasis in the Ileum. Out of a group of more than 200 patients in whom roentgen observations were made six and twelve hours after a barium-potato gruel meal there were 42 without important lesion of the stomach whose small intestines emptied slowly and who had residue in the ileum at the end of twelve or more hours. In 16, the twelve-hour ileal residue was large, in 3 cases persisting until nineteen, forty-eight, and fifty-four hours respectively, in 18 was moderate, and in 8 small; the lesion was chronic appendicitis in 20, adhesions of the ileum or colon in 20, atony and ptosis in 10, disease of the gall-bladder in 2.

Only 4 of these cases showed any delay in emptying the stomach as measured by a six-hour residue.

In 2 the stomach residue at the end of six hours was very small and both were delicate women, over seventy, in whom a slight delay was not remarkable. The other 2 with good-sized residue showed slight deformities near the pylorus, which we interpreted as possible adhesions or spasm.

In short, in nearly all the cases which showed definite or marked delay in emptying the small intestine the stomach emptied promptly. This does not seem to support Barclay's theory of an ileopyloric reflex from the last coils of the ileum to the pylorus to shut off the food supply by closing the pylorus until the ileum is more empty.

The pyloric spasm seen by radiologists in chronic appendicitis is variable and uncertain and has little constant effect on function, the more chronic and quiescent the appendix the less likely it is to cause delay.

Smithies found persistent gastric retention in only a little over 3 per cent. of pyloric spasms associated with appendicitis and cholecystitis; intermittent retention was frequent, and usually disappeared after removal of the appendix or gall-bladder.

Effect of Chemical Irritation of the Bowel. This was tested in cats in the following way: In order to produce irritation in the cecum without any other trauma to the bowel a well-oiled rectal catheter was passed up the colon to the cecum and the irritant injected with a syringe. The short simple colon of the cat makes it easy to pass a catheter, and its exact location was shown with the fluorescent screen. Barium sulphate was mixed with the injected material, so that the amount and place of the injection could be seen.

Twenty-five successive experiments with two different cats showed that injection of turpentine oil, either a few drops or ten drops, or 2 c.c., caused no delay in emptying the stomach. The same result was obtained with a few drops of croton oil. Injection of four or five drops of mixtures of mustard oil and olive oil gave varied results; in 4 instances the cat vomited the whole contents of the stomach promptly after the injections, in 4 cases the injection slowed the emptying of the stomach, evidently in proportion to the strength of the mustard oil, and the irritation produced in the colon. That is, the emptying time of the stomach was delayed from the normal two or three hours to five or six hours. In striking contrast to this, active irritation of the cecum with mustard oil caused *just as often* rapid downward emptying of the stomach and whole digestive tract, both above and below the irritated point.

We may grade the results roughly according to the degree of irritation of the cecum.

1. Intense irritation caused prompt reverse peristalsis in the stomach, with vomiting of its whole contents.

2. Marked irritation caused either (*a*) delay in emptying the stomach up to about twice the normal time, evidently due to spasm of the pylorus, or (*b*) hyperperistalsis and rapid emptying of the stomach and whole digestive tract.

3. Moderate or slight irritation had no effect on the emptying of the stomach.

We did not get a perfect gradation of results, evidently because of the part played by spasm, which was very variable.

Clinical Data in Diseases of the Lower Bowel. Data in the following group of intestinal cases show that delay in emptying the stomach after a barium meal is the exception, not the rule. We need to be careful in studying such a group to allow for some delay due to ptosis and atony of the stomach, which often occurs in thin, weak, or old people.

In 7 cases of chronic colitis there was no delay in emptying the stomach. In 3 cases of tubercular ulceration of the colon there was no delay and the diseased part of the bowel was so irritable that the barium meal passed through it very rapidly, and it appeared empty. This is typical of this disease.

In 5 cancers of the colon, causing more or less obstruction, 2 of the cecum and ascending colon, 2 of the transverse colon, and 1 of the sigmoid, there was no delay. In 1 case of chronic intussusception of the ileum one foot above the ileocecal valve there was no delay. Borbjarg, in studying tumors of the ileocecal region and colon (using the residue six hours after a Riegel meal to test gastric motility, possibly an overdelicate test), suggests that tumors below the cecum do not delay stomach emptying and that tumors in the ileocecal region frequently do.

We have seen that in 42 cases with ileal stasis occurring in chronic appendicitis and adhesions of the ileum and colon only 4 showed any delay in emptying the stomach. In an additional group of 53 cases, 27 with clear evidence of chronic changes about the appendix, 26 with adhesions of the ileum, cecum, or colon, there were only 3 which showed any delay in emptying the stomach, 1 was a case of chronic appendicitis, 2 adhesions. There was one medium and two small five- to six-hour residues.

We had little chance to study acute appendicitis because early operation is usually needed. Two out of 8 cases of acute and subacute appendicitis showed slight delay in emptying the stomach, namely, a small six-hour residue, with the stomach empty at the end of seven or eight hours. This was not conclusive, as we obtained the same results in several other fever cases with pain, in which the bowel was not involved. Our experience with chemical irritants

of the cecum suggest that different degrees of inflammation of the appendix may affect the stomach in a corresponding way by causing vomiting or delay in emptying or rapid emptying, though we have not been able to prove it.

Peritoneal involvement is important. Compare the definite effect on the stomach which Cannon[11] got by performing a laparotomy and injecting croton oil into the cecum by needle through the peritoneum; with the lack of effect we obtained by avoiding the peritoneum and injecting the croton oil by catheter. The element of pain is important; even such a simple lesion as fissure of the anus, if very painful, may cause delay, and a good-sized six-hour residue in the stomach.

In a total of 120 cases of lesions of the lower bowel there were only 9, or 7.5 per cent. which showed any delay in emptying the stomach. Several of these cases were old and weak, and some delay might be expected independent of reflexes from the lower bowel.

Clinical and experimental observation in lesions and irritation of the *upper* bowel (duodenum and jejunum) have shown that they often delay emptying of the stomach; they are outside the scope of this paper.

In conclusion, there is evidently a definite correlation of upper and lower parts of the digestive canal by a protective mechanism which works under a powerful stimulus, such as intestinal injury or surgery or intense irritation, but which does not work under a moderate stimulus or simple mechanical condition. The action of this mechanism is complicated by the contrary results of spasm and hyperperistalsis.

Evidence indicates that the delay in emptying the stomach is the result of impulses through the vagus causing pylorospasm, not inhibition of the motor fibers of the stomach through the splanchnic nerves.

The delay in emptying the stomach caused by spasm of the pylorus is very variable, present one day and absent the next under similar conditions; in general, *marked delay* in emptying the stomach is far more often the result of actual lesions about the pylorus than of reflexes from the bowel.

It is not fair to compare the intestine to a railroad under a block

system where delay low down the line regularly holds up food for several blocks above or to say that "an irritating lesion slows the progress of food coming toward it from above." It may or may not do so, depending on the character and degree of the irritating lesion. It is evident that "stomach symptoms" in intestinal cases are not the result of slow emptying of the stomach, as a rule, but are largely toxic or the result of referred pain or distress.

SUMMARY. The roentgen-ray method was used to study the effect of stimuli from the lower bowel on the rate of emptying of the stomach; the effect of mechanical filling and distention of the colon by enemata in men and cats; the effect of chemical irritation of the cecum in cats; the effect of diseases of the lower bowel in 120 cases of chronic colitis, tubercular ulceration and cancer of the colon, chronic and acute appendicitis, and adhesions of the lower ileum and colon.

Our results all point the same way: (1) delay in emptying the stomach is the exception, not the rule, in lesions of the lower bowel; (2) a strong stimulus is needed from the lower bowel to slow the stomach, for it was found that the stomach emptied a barium meal within the normal time in some cases of ileal stasis of two or more days' duration, and in most cases with good-sized twelve-hour residue in the ileum, also when the colon was distended with a large enema, also in most cases of chronic appendicitis and chronic inflammations and tumors of the colon.

Experiments on animals showed that when the colon was irritated by injections into the cecum variable results were obtained, intense irritation caused vomiting; less marked irritation caused either delay in emptying the stomach up to about twice the normal time, or rapid emptying of the stomach and whole digestive tract; moderate or slight irritation had no effect. The results were not perfectly graded, evidently because of variable spasm.

There is evidently a definite correlation of different parts of the digestive canal by a protective mechanism which works under a powerful stimulus, such as intestinal surgery or injury or strong irritation, but which does not work under a moderate stimulus or simple mechanical conditions. The action of this mechanism is complicated by the contrary results of spasm and hyperperistalsis.

Marked delay in emptying the stomach is far more often the result of actual lesions about the pylorus than of reflexes from the bowel. "Stomach symptoms" in intestinal cases are not, as a rule, the result of slow emptying of the stomach.

II. Some Effects of Massage on the Colon. Abdominal massage is a method freely advised and used in intestinal stasis both general and local. We have felt uncertain about the actual results obtained and wished to verify them by actual observation. Cannon's method of direct examination of the bowel with the roentgen rays was used in studying the human colon at intervals after vigorous abdominal massage (especially of the colon).

The persons examined were vigorous, and without any important disease of the digestive or other organs. They came with a well-filled colon about twenty-four hours after a barium meal, were massaged, and the colon watched at intervals with the roentgen rays and fluorescent screen to see what happened. Deep abdominal massage was given for five to twenty minutes, especially over the course of the colon, both transversely to mash up the contents and to push them along if possible.

There was great variation in different persons in the accessibility of parts of the colon to massage. For example, we especially wished to empty the cecum "the human drain trap," but we found the cecum in all sorts of positions, from deep in the true pelvis (and entirely out of reach) or in the hollow of the ileum and easily accessible, to positions above the ileac crest with only a soft background. Unless one *knew* where the individual cecum was, much effort to directly massage it would be wasted. The transverse colon hung at quite different levels and the splenic flexure was often, and the hepatic flexure at times, well under the edge of the ribs and very hard to reach. The pelvic colon was practically inaccessible.

We see difficulties for the patient in following Sahli's advice to perform automassage with a cannon ball "along the probable course of the colon."

We found that vigorous abdominal massage usually mashed up the contents of the colon but had little or no immediate effect in moving the solid contents forward. Case[12] and Hertz[13] report similar results. This was true of massage of any sort whether

transverse or stripping along the course of the colon. Strong pressure will not move the contents of the ascending colon into the transverse colon or the contents of the transverse into the descending colon. The haustræ by gripping the contents in many places hold it firmly.

If the colon is distended with gas a small lump of contents may occasionally be moved a short distance forward. If the abdominal walls are well relaxed and the bowel forcibly compressed with the fingers in a favorable place, like the ileac fossa, where there is a firm background, a little movement may result. When a full cecum felt as if it were being emptied at once, it was found that gas had moved forward and solid contents merely flattened out in both directions.

We found when the cecum was low, or below the brim of the pelvis, that massage often pushed the tip of the cecum still lower into the pelvis and pushed material farther down into the cecum, filling it fuller than before. This is unfortunate, as these are just the cases in which mechanical help in emptying the cecum is most needed.

These results contrast sharply with the easy statements often found in text-books that "massage pushes along the contents of accessible portions of the stomach and bowel."

It is evident that any favorable effect of massage must be due to increasing the tone of the colon, not by directly squeezing its contents along.

In watching the later results of massage of the colon, at intervals of several hours, it was found that massage sometimes delayed but usually hastened the passage of colon contents, evidently by stimulation of slow peristalsis. For example, we found that massage at 2 P.M. would quite often cause an extra stool at 8 or 9 P.M. in addition to the usual morning stool. The occasional delay after massage was probably due to muscular spasm.

The effect of massage was small in comparison with the stimulus of taking food. That is, the well-known forward movement in the colon after a meal was much greater than we could produce in the same time following vigorous massage of the colon.

A rapid onward "mass movement" of a large portion of colon

contents was seen very rarely (twice) after massage. That is, a part of the colon suddenly loses its haustral markings, forming a sausage-shaped mass which travels rapidly from one part of the colon to another. These large movements had no direct relation to the force of massage; for example, deep massage in one case would give no result, and light palpation would cause a marked mass movement in another. The massage was not a mechanical stripping process, but the stimulus to a reflex mechanism.

SUMMARY. Cannon's method of direct examination of the bowel with the roentgen rays was used in studying the human colon at intervals after giving abdominal massage (especially of the colon).

There was great variation in different persons in the accessibility of parts of the colon to massage.

Vigorous massage usually mashed up the contents of the colon, but had little or no immediate effect in moving the contents forward. When a full cecum was apparently emptied at once it was found that gas had moved forward and solid contents merely flattened out in both directions.

Massage sometimes delayed, but usually hastened, the passage of colon contents at the end of several hours, evidently by stimulation of slow peristalsis. The effect of this stimulus was small in comparison with the stimulus of taking food.

Prompt emptying of any part of the colon by massage is a fallacy; this is especially true of the low cecum, which is usually inaccessible, and is often pushed lower and filled fuller than before. The good effects of massage are found in a mashing up of the intestinal contents and a stimulation of muscular tone and slow peristalsis which usually drive the contents slowly forward for several hours.

I wish to acknowledge my indebtedness to Prof. Walter B. Cannon, of Boston, for valuable help and suggestions, and to Dr. L. B. Morrison, of Boston, for roentgen-ray data in some of the intestinal cases.

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ON THE CONTROL OF THE SYMPTOMS OF DIABETES INSIPIDUS BY SUBCUTANEOUS INJECTIONS OF EXTRACTS OF THE HYPOPHYSIS CEREBRI (PARS POSTERIOR AND PARS INTERMEDIA)*

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Introduction.—To be compelled to pass large quantities of urine at short intervals throughout the day and the night and to be forced to drink correspondingly large quantities of water to slake the thirst are symptoms that may become so tormenting as to make the patient manifesting them a real object of compassion. In severe diabetes insipidus the polyuria may, as everyone knows, be extreme; the quantity of urine passed each twenty-four hours often amounts to 10 or 12 liters, in one case on record it was as much as 43 liters. The specific gravity is very low, the kidneys being unable to excrete a concentrated urine. It is hard for a normal person to conceive of the thirst these patients must suffer, if we are to judge of thirst by the amount of water imbibed. The water intake in Trousseau's famous case reached 50 liters in the twenty-four hours. A patient will sometimes swallow a large pitcherful of water as a single drink and if good drinking-

* Presented under the title The Influence of Pituitrin upon the Urinary Excretion in Diabetes Insipidus.

water be not available, it is astonishing to what lengths a sufferer may go in the effort to quench his thirst; it has been stated that Strubell's patient, deprived of water, drank his own urine!

In the severe cases of diabetes insipidus the patients often become very nervous. The pollakiuria and the polydipsia of the day are troublesome enough but at night they interfere with sleep and few people can experience a prolonged insomnia without growing progressively more disturbed. It is but little wonder then that physicians have sought eagerly for remedies that will mitigate the symptoms of this disease. Many measures have been tried, but, until recently, without success.

It will be clear, however, from the case history to be recorded here, which is in agreement with a few other case histories reported between 1913 and now, that we are now in possession of a method of controlling both the urinary output and the thirst in patients suffering from diabetes insipidus, to their great advantage. That method consists in the subcutaneous administration at certain intervals, of suitable amounts of extracts of the posterior lobe (and pars intermedia) of the hypophysis cerebri. By applying this method the patient's polyuria and polydipsia can be made to disappear and the kidneys will again excrete a urine of normal concentration.

The history of the patient before the hypophysial-extract therapy was applied. Katherine L., single, a teacher of music, aged forty-four, was referred to one of us on February 17, 1917, for special diagnostic study and for treatment, by Dr. Philip S. Roy, of Washington, D. C. She complained of passing very large quantities of urine at short intervals throughout the day and the night, of sleeplessness, of nervousness, of excitability, of trembling of the hands and of palpitation of the heart. On admission to the private ward of the Johns Hopkins Hospital a detailed anamnesis was recorded by Dr. F. H. Kruse, of which the following is a summary.

Family History. Negative for diabetes insipidus. Five sisters died in infancy, but, so far as is known, there has been no luetic infection in the family. The father is living and well at the age of eighty-six. The mother died in childbirth at forty-one. One sister died of pneumonia at thirty-nine. Three brothers and two sisters are alive and well.

Previous History. Aside from some severe febrile disease of unknown nature lasting three months when she was eighteen, the patient was healthy until the summer of 1916, when the present illness began. No excess in

the use of tea, coffee, or alcohol. Menstruation began rather late (eighteenth year); regular; no dysmenorrhea; each period lasts about five days; flow rather profuse, more so since last October.

Present Illness. The patient states that her unusual thirst began in September, 1916. She looks upon the thirst as the beginning of her illness, though in the preceding July and August she had felt very tired and listless. When directly questioned she admitted that for at least two years earlier she had felt fatigue more easily than was her wont and had noticed a lack of her accustomed energy. She had, however, gained weight during the summer (increase of twelve pounds between July and October), but she asserts that she gains weight every summer, and loses in winter.

When the thirst began in September, she rapidly increased her fluid-intake, drinking large quantities of water, lemonade, and orangeade. Before long she found that she was drinking from 8 to 10 quarts of fluid in the twenty-four hours. She craved water and sour drinks, but has no especial desire for sweets. She drank about half of the total fluid at night and the amount of urine voided corresponded closely to the amount of fluid ingested. The frequent voiding interfered with her work during the day and kept her from sleeping at night, so that she grew ever more nervous and distressed. On one day the urinary output was 11 liters and the specific gravity 1001.

In the middle of October, 1916, she became so weak and nervous that she was compelled to relinquish her teaching. At Dr. Roy's suggestion she remained in bed for a few weeks, during which time she was carefully observed, several important diagnostic tests were made, and a variety of therapeutic measures were tried. Aside from palpitation of the heart and some disturbances of digestion (gaseous eructations; abdominal discomfort), there were no symptoms except those already mentioned. There had been no headache, no flushing, no pains in the limbs, no hemianopsia or other disturbance of vision. The Wassermann reaction was negative in the blood serum. Nothing abnormal could be made out on ophthalmoscopic examination. The cerebrospinal fluid obtained by lumbar puncture was found to be normal, and the puncture was followed by severe headache. Contrary to J. B. Herrick's experience and that of Dean Lewis, the polyuria in our case remained uninfluenced by the lumbar puncture.

Dr. Roy treated the patient, applying the several drugs that have been advised for diabetes insipidus, but with disappointing results. Codeia, ergot, and bromides had but little if any favorable effect. For some ten days, 1 grain of thyroid-gland substance and 3 grains of suprarenal-gland substance were administered thrice daily without avail. Even pituitrin was tried and abandoned after a few doses. Most benefit seemed to be obtained from the rest in bed; after it, the patient felt stronger and less nervous; but the polyuria, the pollakiuria, the polydipsia, and the insomnia continued.

About the middle of December, Miss L., was permitted to go to the country and to indulge in gentle exercise in the open air. Though she felt weak and nervous and had gaseous eructations, she ate fairly well and continued to drink from 6 to 8 liters of water daily. In February she was referred to us for special study in the hope that, after experiment, some method of controlling the polyuria and polydipsia might be worked out.

Physical Examination. On admission to the private ward, general physical examinations were made by several members of the staff (Barker, Sprunt, Carter, Kruse) and a number of tests were made by specialists; the findings may be summarized as follows: Height, 5 feet 4 inches; weight, 153 pounds; moderate obesity (calculated ideal weight 132 pounds); temperature ranging between 99° and 100° (became normal after five days in the hospital); moderate tachycardia, pulse varying between 90 and 115 (the rate dropped, and after the first week varied between 76 and 83).

Bony framework, medium; acra of head, rather prominent; roentgenogram of sella turcica, normal; some spacing of the upper incisors; tendency to prognathism; rather marked kyphosis of middorsal spine, but no gibbus; thorax slightly emphysematous in type; pelvis broad.

Skin clear, soft, but rather dry; some pigmentation of the face and especially of the eyelids; hair of head, iron gray, abundant; eyebrows, heavy; long eyelashes; a few hairs on chin and upper lip; hirci and crines abundant and of normal feminine type; subcutaneous fat somewhat excessive, being especially abundant over the back of the neck and in the region of the breasts, though fairly evenly distributed elsewhere; in the extremities, the fat is proximally, not distally, distributed; no edema; tendency to erythema of neck, upper chest, and back.

Muscles well developed; some fine tremor of the fingers; no muscular atrophy. Joints normal. Lymph glands normal.

Pulse accelerated (*vide supra*); radial arteries just palpable, only slightly thickened; blood-pressure on admission 210 systolic, 120 diastolic; it fell gradually until on March 1 it was 175 systolic, 105 diastolic; between March 1 and March 25 the systolic pressure varied between 175 and 185, and the diastolic between 105 and 118. Heart only slightly enlarged; apex beat forcible; aortic second sound loud and ringing; no heart murmurs. No retrosternal dulness. Lungs negative on physical and on roentgenographic examination. Thyroid slightly but definitely enlarged, not pulsating.

Teeth spaced. Infection of the right upper second and third molar roots and of the right lower first bicuspid. Many cervical erosions. Gingival hypertrophy (Dr. C. J. Grieves).[1] Examination of digestive tract otherwise negative. Large mass palpable in abdomen (*vide infra*).

[1] The infected teeth were extracted and the sockets curetted. The gums were treated.

Urine on admission: pale, day urine 4640 c.c., night urine 3650 c.c., total 8290 c.c. Urine voided almost hourly in amounts ranging from 175 to 560 c.c., slightly acid, specific gravity 1001 to 1004; occasionally a faint trace of albumin present; no casts, a few white blood corpuscles seen. Phthalein output, first hour 58 per cent., second hour 10 per cent., total 68 per cent.; Amhard's K. = 0.221; urea N in 100 c.c. blood = 11 mgm. (For other special studies of the urine in the Chemical Division of the Laboratory of the Medical Clinic, *vide infra.*)

The kidneys were not palpable. No signs of renal, ureteral, or vesical calculus. External genitals normal. On vaginal examination (Dr. Cullen), cervix uteri small, large myomatous uterus, mass extending upward almost to umbilicus, freely movable.

Blood count: red blood corpuscles, 5,312,000; white blood corpuscles, 13,500; hemoglobin, 76 per cent. (Sahli); no parasites.

Wassermann reaction in blood serum negative.

Nervous system: sensation normal; motility normal; deep reflexes markedly exaggerated but equal on the two sides; superficial reflexes normal; coördination normal; psyche, restless and excitable at first when suffering from lack of sleep. Stereoscopic *x*-ray of skull showed "marked increase of vascularity, especially in the frontal region" (F. H. Baetjer and C. A. Waters).

Eyes: pupils equal; react to light and accommodation; extraocular movements normal. Slight protrusio bulborum. v. Graefe, Dalrymple and Rosenbach signs positive; Moebius' sign negative. Ophthalmoscopic examination (Dr. Lloyd Whitham):—nearly negative. Possibly slight temporal pallor. Vessels in both eyes somewhat attenuated. Visual fields nearly normal though there is some interlacing of the outlines of the fields for red and green.

Diagnosis. Diabetes insipidus; dyshypophysism; hyperthyroidism; oral sepsis; arteriolar sclerosis with arterial hypertension and arteriolar nephropathy; myoma uteri.

Brief Review of Some of the Newer Publications on Diabetes Insipidus. One has only to consult Futcher's careful review of diabetes insipidus in the second edition of Osler and McCrae's *Modern Medicine* (1914) to see how many methods of treatment have been tried without success and to learn how unsatisfactory our knowledge of the real nature and pathogenesis of the disorder has been until very recently. The dangers of restricting the fluid intake of the patient are now generally appreciated. Exceedingly interesting observations were made by Tallqvist (1903), E. Meyer (1905–1912) and others, which indicated that the kidneys in diabetes insipi-

dus are incapable of excreting a concentrated urine, and since their studies some authors have spoken of a "renal type" of the disorder. Careful studies of renal function made by R. Fitz (1914) in Henry Christian's Clinic at the Peter Bent Brigham Hospital in Boston showed that "the kidney as a whole was normal, but gave findings characteristic for vascular hyposthenuria with vessels hypersensitive to chloride stimulation." Fitz concluded that the disease, at least in the case he studied, was "probably not due to a primary lack of ability to concentrate on the part of the kidney." In 1917 J. H. Barach, of Pittsburgh, reported a case in which the output was 11 liters, but the kidney could concentrate, though only slightly, on increased ingestion of salt and urea.

Two great steps forward were made (1) when the experimental physiologists (E. A. Schäfer and his colleagues Magnus and Herring) began to recognize the effects of a hormone from the hypophysis cerebri upon urinary excretion and (2) when clinicians and pathological anatomists discovered the frequent association of diabetes insipidus with lesions at the base of the brain, especially with lesions (natural or experimental) involving the hypophysis cerebri (E. Frank, 1912; H. Cushing, 1913). The earlier physiological work had indicated that injections of extract of the pars posterior (and pars intermedia) of the hypophysis cerebri caused diuresis in experimental animals. When, therefore, the clinicians and pathologists discovered the frequent association of diabetes insipidus with lesions of the hypophysis cerebri, they put forward the theory, based upon a too uncritical acceptance of the results of the physiologists, that diabetes insipidus is due to a hyperfunction of the posterior (and intermediate) parts of the hypophysis. At times the clinicians were hard put to it to make their observations fit in with this hypothesis, especially when destructive lesions (neoplastic; surgical) were found to be associated with prolonged polyuria, a discrepancy in ideas that did not escape A. Biedl (1913). The known association, sometimes, of diabetes insipidus with dystrophia adiposogenitalis, the latter known to be due to hypofunction of the hypophysis, should also have shaken faith in the view that diabetes insipidus is due to hyperfunction of the hypophysis. A third important step forward was made by Pentimalli and Quercia in 1912. These investigators

found that in the isolated kidney of the rabbit, perfused with Ringer's solution, posterior lobe extract caused constriction of the renal vessels and diminution of the urinary outflow. A fourth step forward, in our opinion a huge stride, was made in 1913 by Farini in Italy, and by von der Velden in Germany. Farini was able to reduce polyuria in two cases of diabetes insipidus and looked upon the disease as due to insufficiency of the hypophysis. The internist, R. von der Velden, working in A. Hoffmann's clinic in Düsseldorf, undertook a revision of the subject of the relation of diuresis in human beings to the injection of hypophysial extracts. This investigator found that, in human beings with healthy kidneys, the injection of posterior-lobe hypophysial extracts did not increase but, on the contrary, diminished diuresis.[1] In patients suffering from chronic nephroses, he met with a similar reaction to injections of posterior-lobe extracts; diuresis was never increased; the excretion of both water and NaCl by the kidneys was diminished. While conducting these experiments, a man suffering from diabetes insipidus came, luckily enough, under von der Velden's observation, and he decided to try in this patient the effects of injections of posterior-lobe extracts. He used pituitrin, hypophysin, and pituglandol (the posterior-lobe extracts supplied by different commercial firms) and discovered that all three would compel the kidneys to double or triple the concentration of the urine and to excrete less water in the urine. Indeed, the curves accompanying his article show that on the days when two injections of pituitrin were administered the urinary output became practically normal. Associated with the disappearance of the polyuria the thirst disappeared, the body weight increased, the patient felt better generally, the feeling of dryness of all the mucous membranes vanished and the appetite improved. The patient had to get up only once or twice at night instead of eight to ten times to urinate. But as soon as the injections were left off, the symptoms reappeared in full severity. Though this author declined at the time to offer an explanation of the mode of action of the pituitrin, and especially stated that "there is little

[1] In the next year (1914) Motzfeldt also found he could check diuresis in a series of fifteen relatively healthy patients by injecting pituglandol whereas anterior-lobe extracts did not exert this effect.

in favor of the idea of a substitution therapy," his clinical-experimental studies were the first to show that substances derived from the posterior (and intermediate) parts of the hypophysis cerebri injected subcutaneously into human beings can make the symptoms of diabetes insipidus disappear as if by magic.

Von der Velden's report has been followed by reports from other clinicians, recording similar results in the treatment of diabetes insipidus. We may mention the articles by Farini (1913), Römer (1913, 1914), Biach (1914), Frey and Kumpiess (1914), Umber (1914), Falta (1915), E. Graul (1915), Hoppe-Seyler (1915), Kleeblatt (1915), von Konschegg and Schuster (1915), H. Strauss (1916), K. Motzfeldt (1916), H. Bab (1916), H. Bab (1916–17), and G. Marañon (1917).

At about the time our patient entered the hospital for study the papers by Bab (1916–17) and by Motzfeldt (1917) came into our hands. In Bab's article, the bibliography is thoroughly and critically sifted; his paper, in our opinion, is especially valuable for its careful presentation of the whole subject from the physiological, pathological-physiological, and clinical-experimental sides. Bab concludes that the hypophysis cerebri must be regarded as the central regulatory station for the control of the physiological functions of the urogenital system, that diabetes insipidus is the result of a hyposecretion of the pars intermedia (or, sometimes, of a disturbance of the reception of the secretion in the pars posterior, or of the propagation of the secretion in the cerebral lymph lacunæ). He believes that the kidneys in themselves are healthy in diabetes insipidus, but that their power to excrete a concentrated urine fails because of the lack of the secretion from the pars intermedia of the hypophysis; the kidneys function normally again if the secretion (from an external source) is supplied through subcutaneous injections. A hyperfunction of the hypophysis cannot be the cause of diabetes insipidus. In Motzfeldt's paper, a series of most interesting experiments carried on in the laboratory of Harvey Cushing's clinic are fully reported. Motzfeldt believes that the discrepancies in the results reported by physiologists are due to the methods employed. In the early experiments (Magnus and Schäfer) anesthetized animals were used and diuresis followed injection of pos-

terior-lobe extracts. In his own experiments Motzfeldt used rabbits, kept quiet, without anesthesia, by placing them upon their backs. Artificial polyuria following the injection of water into the stomachs of these rabbits is definitely checked by subcutaneous injection of posterior-lobe extracts. The effect could be obtained constantly and was proved to be independent of intestinal absorption and of vagal influences. It could be prevented by section of the splanchnics or of the renal nerves near the hilus of the kidney. Motzfeldt concludes that the secretion of the pars intermedia of the hypophysis exerts its antidiuretic effect through stimulation of the sympathetic nerves, influencing especially the renal vasomotor system.

Results of Therapy Personally Observed. As we have pointed out above, the treatment of diabetes insipidus by various methods, such as restriction of the fluid intake, antiluetic therapy and spinal puncture, has not been consistently successful. It was only when the subcutaneous (or intravenous) injection of the extract of the posterior lobe of the hypophysis was employed that the much-sought-for relief from this affliction was obtained. Thus far comparatively few cases treated by this method have been reported, and on account of the small number of observations recorded, it would seem essential that the value of hypophysial extracts in this connection should be substantiated. It might very well be that diabetes insipidus is a syndrome that can be produced not only by insufficiency or other derangement of hypophysial function but also by other pathological processes. If this should turn out to be true, ultimately instances of the disease would be met with in which the injection of hypophysial extract would not reduce the increased urinary excretion, and a still clearer conception of the mechanism of what have, until a short time ago, been considered idiopathic polyurias would be arrived at. The treatment of the patient, detailed in this communication, yielded results that did not differ appreciably from those reported by other authors who have injected posterior-lobe extracts. The facts given may therefore be considered as confirming previous observations.

Our patient, K. L., was kept throughout her stay in the hospital on a fairly constant diet, low in salt and protein; water was allowed in any quantity desired. In Table I are given the hourly volume

and the salt and the nitrogen concentration of the urine before any treatment other than the dietary restriction, mentioned above, was instituted.[1] It will be seen from Table I that even when the food contained but a small amount of material yielding end-products that are excreted by the kidneys this patient voided a urine, the twenty-four-hour volume of which was above 8000 c.c. and in which the hourly quantity rose, at times, as high as 560 c.c.; the maximum of salt concentration was only 0.13 per cent., and that of the nitrogen concentration 0.14 per cent.; the specific gravity varied between 1002 and 1004. Further tests performed under similar conditions yielded practically identical results.

TABLE I.—Hourly Specimens and Analyses of Urine Uninfluenced by Medication.

	Time.	Urine.					
		Volume.	Specific gravity.	NaCl.		N.	
	A.M.	c.c.		per cent.	grams.	per cent.	grams.
1	8– 9	360	1002	0.05	0.18	0.07	0.25
2	9–10	245	1003	0.04	0.10	0.07	0.17
3	10–11	560	1002	0.05	0.28	0.06	0.34
4	11–12	390	1003	0.05	0.20	0.07	0.27
	P.M.						
5	12–1	485	1003	0.05	0.24	0.06	0.29
6	1–2	455	1003	0.05	0.23	0.07	0.32
7	2–3	280	1003	0.02	0.06	0.05	0.14
8	3–4	290	1003	0.02	0.06	0.14	0.41
9	4–5	360	1003	0.01	0.04	0.08	0.29
10	5–6	280	1003	0.13	0.36	0.08	0.22
11	6–7	175	1004	0.04	0.07	0.07	0.12
12	7–8	375	1003	0.12	0.45	0.08	0.30
13	8–9	385	1003	0.02	0.08	0.07	0.27
Total day		4640	....	....	2.35	....	3.39
9 P.M. to 7 A.M. . . .		3650	1003	0.05	1.83	0.07	2.56
Total 23 hours		8290	.....	....	4.18	....	5.95

In carrying out the treatment by subcutaneous injection, two preparations were used: "pituitrin" and "pituitary liquid." Both of these are extracts of the pars posterior (and pars intermedia) of the hypophysis cerebri (or pituitary body), the former being the product of Parke, Davis & Company, the latter of

[1] The nitrogen was determined by the Kjeldahl process, and the sodium chlorid according to Volhard, in all the tests.

Armour & Company. One preparation apparently is as efficacious as the other. The response of the kidneys to numerous injections was constant throughout, and only a few typical examples are given. The most favorable effect was obtained when two or more injections of not less than 1 c.c. each, of either preparation, were given during the course of the day. It may be noted that, in Table II, the second injection was much more potent than the first

TABLE II.—Note the Marked Effect of the Second Injection of "Pituitary Liquid" in Producing Oliguria, in Raising the Specific Gravity, and in Increasing the Concentration of N and of NaCl. Two Injections of 1 c.c. of Either "Pituitrin" or "Pituitary Liquid" during Twenty-four Hours Constituted the Minimal Dosage and the Smallest Number of Injections that were Efficacious in This Patient.

Time of day.	Urine.					
	Volume.	Specific gravity.	NaCl.		N.	
	c.c.		per cent.	grams.	per cent.	grams.
8–10 8.30 A.M.*	390	1005	0.18	0.70	0.13	0.51
10–12	210	1008	0.24	0.50	0.10	0.21
12– 2	188	1007	0.14	0.26	0.21	0.39
2– 4 3.45 P.M.*	295	1005	0.06	0.18	0.15	0.44
4– 6	85	1013	0.55	0.47	0.41	0.35
6– 8	95	1010	0.16	0.15	0.43	0.41
Total day	1263	....	....	2.26	....	2.31
Night, 8–8	1430	1005	0.30	4.29	0.16	2.29
Total 24 hours . . .	2693	....	....	6.55	....	4.60

in reducing the polyuria, in increasing the specific gravity, and in raising the salt and nitrogen concentration in the urine. From 4 to 8 P.M. the urine of this patient when thus influenced was not very different from that of a normal person. The effect, however, was not a lasting one, since, even in the urine voided a few hours later during the night, there was distinct evidence that the influence of the injected hypophysial extract was rapidly diminishing. With two injections of 1 c.c. each during the day, this patient was made perfectly comfortable, and apparently the efficacy of the extract did not diminish over a period of four weeks' trial in the hospital

* 1 c.c. "pituitary liquid" intramuscularly.

nor after about one month's continuation of the therapy at home. The patient having once experienced the relief afforded by the injections refused to do without them. On days when other modes of therapy were being tried, she complained bitterly of the symptoms and begged for the injection of the hypophyseal extract.

TABLE III.—The Result of a Single Injection of "Pituitary Liquid." The Effect was only Temporary, and did not Relieve the Patient Much.

Time of day.	Urine.					
	Volume.	Specific gravity.	NaCl.		N.	
	c.c.		per cent.	grams.	per cent.	grams.
9–11 11 A.M.*	515	1003	0.02	0.10	0.10	0.52
11–1	154	1010	0.45	0.69	0.19	0.29
1–3	164	1006	0.15	0.25	0.27	0.44
3–5	112	1006	0.04	0.04	0.40	0.45
5–7	600	1003	0.04	0.24	0.11	0.66
7–9	520	1003	0.02	0.10	0.10	0.52
Total day	2065	....	....	1.42	....	2.88
Night, 9–9	5240	1003	0.06	3.14	0.07	3.67
Total 24 hours . . .	7305	....	....	4.56	....	6.55

TABLE IV.—Very Transient Therapeutic Results with 0.5 c.c. Doses of "Pituitrin."

Time of day.	Urine.					
	Volume.	Specific gravity.	NaCl.		N.	
	c.c.		per cent.	grams.	per cent.	grams.
9–10	540	1002	0.02	0.11	0.07	0.38
10–11	770	1002	0.14	1.08	0.04	0.31
11–12	620	1002	0.02	0.12	0.05	0.31
12– 1 12.10 P.M.†	28	1004	0.19	0.05	0.19	0.05
1–3	120	1007	0.11	0.13	0.08	0.10
3–5 5 P.M.†	470	1003	0.21	0.99	0.13	0.61
5–7	90	1010	0.10	0.09	0.41	0.37
7–9	288	1005	0.03	0.09	0.22	0.63
Total day	2926	....	....	2.66	....	2.76
Night, 9–9 10 P.M.†	5160	1003	0.11	5.68	0.07	3.61
Total 24 hours . . .	8086	....	....	8.34	....	6.37

* "Pituitary liquid" 4 c.c. intramuscularly.
† "Pituitrin" 0.5 c.c. intramuscularly.

The questions now arise: May the quantity of the extract used be diminished, and, may the intervals between injections be prolonged? We must answer, No; not without seriously interfering with the patient's comfort. A single injection, even if it were a large one, was repeatedly found to be inefficient. In Table III the influence of a single injection of 4 c.c. is seen to have lasted but four hours, and did not afford the patient very much relief. Injections of amounts smaller than 1 c.c. failed to yield any but very transient therapeutic results (Table IV). On seventeen days injections of "pituitrin" or of "pituitary extract" were given at varying intervals and in different doses and the results carefully observed. The above three examples (Tables II, III and IV) represent the practical results that were obtained.

TABLE V.—Data from Urinary Specimens Collected in the Course of Twenty-four Hours. "Tethelin" (Prepared from the Anterior Lobe of the Hypophysis by Dr. T. Brailsford Robertson) was Injected Liberally and Apparently without Effect. A Single Injection of "Pituitrin" Given at 1 A.M. in Order that the Patient Might Get Some Sleep was Probably Responsible for the Slightly Increased Concentration of Salt in the Night Specimen.

Time of day.	Urine.					
	Volume.	Specific gravity.	NaCl.		N.	
	c.c.		per cent.	grams.	per cent.	grams.
8 A.M.* 9.00–10.20	610	1003	0.06	0.37	0.09	0.55
10.20–11.00	680	1002	0.08	0.54	0.10	0.68
11.00–12.55	595	1002	0.02	0.12	0.07	0.42
12.55–3.00 1 P.M.*	590	1003	0.04	0.24	0.10	0.59
3.00–5.00	670	1003	0.04	0.27	0.07	0.47
5.00–7.00 6 P.M.*	420	1003	0.04	0.17	0.11	0.46
7.00–8.15	550	1002	0.02	0.11	0.08	0.44
8.15–9.00	440	1002	0.01	0.04	0.07	0.31
Total day	4555	....	....	1.86	....	3.92
Night, 9–10 P.M.* 1 A.M.†	5220	1003	0.17	8.87	0.08	4.18
Total 24 hours . . .	9775	....	....	10.73	....	8.10

* 100 mgm. "tethelin" subcutaneously. † "Pituitrin," 1 c.c. subcutaneously.

Injections of the anterior lobe of the hypophysis, in the form of "tethelin," kindly supplied by Dr. T. Brailsford Robertson, of San Francisco, were without effect (Table V). The same was true of injections of "adrenalin" (Table VI).

TABLE VI.—The Injection of "Adrenalin" did not Influence the Urinary Secretion.

Time of day.	Urine.					
	Volume.	Specific gravity.	NaCl.		N.	
	c.c.		per cent.	grams.	per cent.	grams.
9.00–10.00	300	1003	0.04	0.12	0.06	0.18
10.00–11.00	465	1002	0.04	0.19	0.07	0.33
11.00–11.30*	275	1003	0.04	0.11	0.04	0.11
11.30–12.30	550	1002	0.03	0.17	0.05	0.28
12.30– 1.00	290	1002	0.05	0.15	0.05	0.15

TABLE VII.—Urine Analyses from Specimens Collected during a Day on which "Pituitary Tablets" were Given by Mouth in Large Doses. The Results do not Show any Improvement over the Period when no Medicine was Given (See Table I).

Time of day.	Urine.					
	Volume.	Specific gravity.	NaCl.		N.	
	c.c.		per cent.	grams.	per cent.	grams.
6 A.M.† 9.00–10.00	485	1003	0.09	0.44	0.06	0.29
10.00–11.00 10 A.M.†	610	1003	0.03	0.18	0.03	0.18
11.00–11.45	480	1004	0.06	0.29	0.03	0.14
11.45– 1.00	540	1004	0.06	0.32	0.05	0.27
1.00– 2.00	435	1003	0.03	0.13	0.06	0.26
2.00– 3.00 2 P.M.‡	515	1003	0.03	0.15	0.06	0.31
3.00– 4.15	565	1003	0.02	0.11	0.05	0.28
4.15– 5.00	265	1004	0.02	0.05	0.07	0.19
5.00– 6.00 6 P.M.‡	405	1003	0.04	0.16	0.06	0.24
6.00– 7.00	440	1003	0.04	0.18	0.06	0.26
7.00– 7.50	415	1003	0.04	0.17	0.07	0.29
7.50– 9.00 8 P.M.‡	600	1003	0.03	0.18	0.05	0.30
Total day	5755	....	....	2.36	....	3.01

* "Adrenalin" (1 : 1000), 10 minims, subcutaneously.

† Six tablets by mouth. ‡ Four tablets by mouth.

NOTE.—Each tablet contained $\frac{1}{10}$ grain extract of the posterior lobe of the pituitary body.

TABLE VIII.—"Pituitary Liquid" (Administered by Soaking it up in Cotton and Placing it Under the Tongue). No Changes in the Urinary Secretion were Noticeable.

Time of day.	Urine.					
	Volume.	Specific gravity.	NaCl.		N.	
	c.c.		per cent.	grams.	per cent.	grams.
9–11 9 A.M.*	490	1003	0.06	0.29	0.10	0.49
11–1	700	1003	0.04	0.28	0.07	0.49
1–3 1 P.M.*	505	1003	0.04	0.20	0.11	0.56
3–5	780	1003	0.02	0.16	0.08	0.62
5–7 5 P.M.*	470	1003	0.04	0.19	0.11	0.52
7–9 9 P.M.*	760	1001	0.02	0.15	0.08	0.61
Total day	3705	....	....	1.27	....	3.29
Night, 9–9	6140	1004	0.09	5.53	0.05	3.07
Total 24 hours . . .	9845	....	....	6.80	....	6.36

Administration of the extract of the posterior lobe by mouth in tablet form, even in fairly large doses, did not prove to be of value (Table VII). Inasmuch as some drugs are absorbed more readily by the mucous membrane of the tongue and mouth than when they are swallowed, this procedure was resorted to, but without any observable favorable influence (Table VIII).

Motzfeldt, on the other hand, was able to check the polyuria in his cases by feeding the fresh posterior lobe obtained from the ox. In his experiments on rabbits he checked diuresis by oral administration but gave relatively enormous doses—fifty times the dose that was efficient on subcutaneous administration.

SUMMARY. The urine of patients suffering from diabetes insipidus may be diminished in amount, its specific gravity can be raised, and the percentage of sodium chlorid and of nitrogen that it contains can be increased by injections of the extract of the pars posterior (and pars intermedia) of the hypophysis cerebri. To afford the patient appreciable relief from the polyuria, it is necessary to administer the "pituitrin" or "pituitary liquid" by subcutaneous injection and to give not less than two doses of at least 1 c.c. each

* "Pituitary liquid" 1 c.c., on cotton, under the tongue.

in the course of every twenty-four hours. These extracts do not lose their efficiency when given daily over a long period. Administration by mouth was without effect. "Tethelin" and "adrenalin" do not seem to be of any value in the treatment of diabetes insipidus.

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DISCUSSION

Dr. Miller said the application of extracts from the posterior lobe of the pituitary body upon diabetics was very interesting. Four or five years ago there was placed on the market a preparation based upon the reported action of the extract from the posterior lobe on certain species of laboratory animals. In certain varieties of these animals there is a diuresis following its ingestion, on the second day, in the majority of cases. In man, however, the drug, either in the normal or in the diseased individual, always causes a reduction in the urinary output. He, too, had used this remedy in a case of diabetes insipidus, with results similar to those of the authors. He had given his patient an intravenous injection of about 0.5 c.c. of the pituitrin, and the patient had a terrific headache thereafter, but reported that for the first time in eight years (that is, during the duration of his diuresis) he had not arisen during the night to urinate.

He, too, had tried very large doses of pituitrin by mouth without effect, also a preparation of the anterior lobe put out by the Parke, Davis & Company was used intramuscularly without effect. He noted from the reports of Drs. Barker and Mosenthal that it is the posterior lobe that is affected in these cases.

Dr. Futcher said it was in 1674 that Thomas Willis first differentiated between diabetes mellitus and diabetes insipidus. It is only within the last four or five years, however, that the true conception of diabetes insipidus has been acquired. In 1912 Frank reported a case of diabetes insipidus in a man who had been shot, and in whom the roentgenogram demonstrated that the bullet had lodged in the sella turcica. He showed that the

kidneys were incapable of secreting a concentrated urine. In 1913 Simmonds reported an instance of the disease in a woman who two months before had been operated on for carcinoma of the breast, the autopsy revealing the fact that a carcinomatous metastasis had destroyed the posterior lobe of the pituitary gland. It pressed upon the pars intermedia of the posterior lobe. Several similar observations, in which the posterior lobe of the pituitary was found involved in this disease, have been reported. In 1905 Eric Meyer advanced the view that diabetes insipidus was due to an inability of the kidneys to concentrate urine. That theory served well for a considerable time; and it was only when these later observations became reported that apparently the true etiology of the disease became evident. Meyer, himself, at a later date, reported a case of the disease in a patient who had dystrophia adiposogenitalis and bitemporal hemianopsia, in which he also showed that the kidneys were unable to concentrate urine. This inability to concentrate urine has been found to exist in practically all the pituitary cases. The polyuria seems to be caused by a disturbance of the functions of the pars intermedia of the posterior lobe.

The sum of the investigations that have been made with pituitrin as a therapeutic remedy seems to be that its injection diminishes the urine output, increases the specific gravity, and increases the ability of the urine to concentrate salt, that is, to eliminate salt and nitrogen. Its effect lasts usually only two to four hours, so that several hypodermic injections daily are necessary.

It is important to recall what Cushing has observed in his series of tumors of the pituitary glands. In 1912, in his Shattuck lecture, he reported 110 cases of pituitary tumor, and he emphasized the point that a great many of these patients had a marked polyuria; six of them had come to him with a diagnosis of diabetes insipidus without the true basic cause having been recognized. Cushing also advanced the rather interesting view that it is quite possible that in many of the functional (or hysterical) polyurias the latter may be due to the stimulation of the hormone of the pituitary gland through the autonomic nervous system.

The speaker asked Drs. Barker and Mosenthal how they explained, on the basis of the pituitary theory of the causation of diabetes insipidus, the remarkable cases of hereditary diabetes insipidus, the so-called essential cases. Weil has reported 91 cases of the disease in generations in one family. Is the pituitary theory likely to hold only for the secondary or symptomatic cases?

Dr. Meltzer said the gratifying fact that we may possess in these substances a therapeutic remedy for diabetes insipidus does not justify any definite conclusion that the pituitary body is the seat of the cause of this disease. We have to distinguish between the function of an organ and the possible therapeutic action of its substances. This is well illustrated just

by the pituitary body. The removal of its anterior part causes the death of the animal, which signifies that the anterior part contains the principle which is indispensable for maintenance of life. At the same time we know that extracts made from that part of the hypothesis are inert, they produce neither physiological nor therapeutic effects. On the other hand, the removal of the posterior part does no harm to the animal; at the same time it is the extracts of just this part which are capable of producing physiological and therapeutic effects.

Dr. Meltzer asked whether Dr. Mosenthal or other investigators have studied the tonicity of the blood in diabetes insipidus. It is conceivable that in this disease the blood and the tissue fluids of the body contain more salt than normal, which makes these patients drink a great deal; and since water in itself is a diuretic, it may cause a considerable secretion of a dilute urine which will not reduce the hypertonicity of the blood. Dr. Meltzer propounded no new theory; he merely asks for information whether the tonicity of the blood has been studied in cases of diabetes insipidus.

Dr. Solis-Cohen said that for the past year he had had under observation two cases of diabetes insipidus, one of which presented a rather interesting feature. The patient was a man of some thirty years of age, a master mechanic in the Pennsylvania Railroad shops. In addition to passing about 10 to 11 liters, that is 10,000 to 11,000 mils. of urine daily, he complained of severe pain in the left hypochondrium. The speaker put him on carbohydrate-free diet, codein and pituitrin. The quantity of urine passed was much diminished—to about 6000 mils.—and the symptoms generally improved. But the pain persisted so severely that a surgical consultation was called. They were unable to make out what definite lesion existed, but concluded that surgical exploration was necessary. Both *x*-rays and symptoms indicated adhesion between the colon and the stomach; but the cause of it was not evident. Dr. Chalmers Da Costa operated and broke up the adhesions, finding nothing else. The output of water fell, without any medication, to about 2 liters per day; but after a month it began to mount up to 4000; 6000; and finally reached again 11,000 mils. The man was once more put upon the pituitary medication, with a resulting constant output of between 3000 and 4000 mils. a day on ordinary diet; and about 2000 mils. on carbohydrate-free diet.

The other patient was a girl of about eighteen or nineteen years of age, belonging to one of those families wherein the speaker had taken so much interest. Her father is tuberculous, her sister had exophthalmic goiter, and many of her relatives exhibited other forms of endocrine and autonomic disturbance. Her greatest output was about 8 liters per day. On pituitary medication it fell to 2 liters per day. Just as in the cases described by Dr. Barker and Dr. Mosenthal, the only effective method was the intramuscular injection.

Dr. McPhedran referred to a case in which the effect of the administration of pituitrin was remarkably pronounced. If the disease is organic, doubtless the treatment will require to be continued, just as in the case of myxedema and cretinism.

Dr. Koplik said he knew of no more difficult subject to study and discuss than diabetes insipidus. Dr. Bookman and he had for the last six years been working on diabetes insipidus, having so far collected three cases, and at that moment had in the ward another case on which they were about to begin treatment. It seemed to him very difficult to separate the two classes of cases. There was a primary polydipsia, or polyuria, or both. This new therapy may apply only to a certain set of cases. Children pass fully the amounts of urine that the adults do, but do not seem to be much affected in their general weight or condition. They had never limited the amount of water taken in by the children and could never say what the effect would be of such a procedure, whether by limiting the quantity of water the children would do worse or dangerous symptoms would be precipitated by the limitation of the water intake.

He did not intend to discuss so brilliant a paper as that of Dr. Barker and Dr. Mosenthal without close study, and would merely suggest that possibly their therapy would eventually apply to only a certain set of cases.

Dr. Mosenthal said that since this patient was very nervous and could only be induced to remain in the hospital with the greatest difficulty, no studies of the blood were attempted, and that he was therefore unable to give an answer to some of the questions asked.

Dr. Barker (closing) said that Dr. Mosenthal and he had not tried the intravenous method of administration to which Dr. Joseph Miller had referred. It might be wise to use it in the evening to ensure a good night for the patient. The nights of those suffering from diabetes insipidus are dreadfully disturbed because of the frequent urination. As Dr. Mosenthal had said the patient cried for pituitrin as a drug-habitué would cry for morphin in order to get a night of sleep.

The observations of Eric Meyer, to which Dr. Futcher had referred, are still as true as they were when they were made; he observed that the kidney in diabetes insipidus is incapable of secreting a concentrated urine, and, to that extent, a nephropathy exists. It is a functional nephropathy due to the failure of arrival in the kidney of a normal regulatory influence on renal secretion. If you administer pituitrin this regulatory influence is supplied. The disorder is not primary in the kidneys; it arises elsewhere; the disturbance of the kidneys is merely functional or dynamic rather than structural.

Dr. Futcher had also pointed out that both diabetes mellitus and diabetes insipidus have turned out to be endocrine disturbances, an exceedingly

interesting point. Diabetes mellitus is due to the failing function of an endocrine organ—the islands of Langerhans; diabetes insipidus is due to the failing function of another endocrine organ—the pars intermedia of the hypophysis cerebri. Dr. Meltzer had commented upon the therapeutic evidence favoring the view that the "site of the disease" in diabetes insipidus is the hypophysis cerebri; but we have something more than the effects of therapy to give us clues to the site of the changes that account for the disease. In a majority of cases of diabetes insipidus that have come to examination postmortem recently changes have been found in the hypophysis cerebri or in its neighborhood. Tumors of the pituitary or of the tuber cinereum may be associated with diabetes insipidus; so also may be luetic basilar meningitis. A case has come to autopsy in which there was a carcinoma metastasis in the pituitary body and in which there had been diabetes insipidus during life. Moreover, the experimental surgeons (Cushing and others) were astonished to find polyuria follow extirpation of the pituitary body, especially the posterior lobe, for from the earlier experiments they had anticipated that an oliguria would result. All these points strongly support the view that the pituitary body is the actual "site of the disease" in diabetes insipidus.

Dr. Koplik referred to the dangers of limiting the water intake in diabetes insipidus. Of course such limitation was risky before the pituitrin therapy came into use. Since the renal disturbance consists of an inability to concentrate, we could formerly influence the polydipsia and the polyuria with safety only by limiting the salt intake and the protein intake, inasmuch as such limitation diminishes the solids of the urine (NaCl; urea) and so diminishes the necessary water output when the specific gravity of the urine is compulsorily low. Now that we can restore the power of the kidneys to excrete a concentrated urine with pituitrin, we can with safety limit the water intake.

Cases of primary polydipsia associated with polyuria independent of true diabetes insipidus probably do exist. They are nearly always psychopathic cases; but one can easily differentiate, usually, between those cases and cases of true diabetes insipidus. If you limit the water intake in the primary polydipsia cases, the concentration of the urine immediately increases; the specific gravity of the urine rises; there is no inability of the kidney to excrete solids in the urine; whereas, in the true diabetes insipidus cases, with the kidney unable (in the absence of sufficient pituitrin-supply) to secrete a concentrated urine, if you limit the water intake and thus limit the water output in the urine, the latter will still have a low specific gravity, a low concentration in salt and in urea; and if you continue to limit the water intake, the patient will become intoxicated and finally will die because of salt retention and of urea retention.

In regard to the prognosis to which Dr. McPhedran had referred, it is probable that in cases where the pars intermedia (or the posterior lobe) has

been destroyed, the pituitrin therapy would have to be carried on as long as the patients live. The speaker believed there were some cases recorded where the disturbance had passed off and one could assume that those were functional (non-destructive) disturbances, of the pars intermedia, or of the pars posterior. There is no evidence that the posterior lobe, itself, is responsible for the manufacture of the secretion. It is the pars intermedia, namely, the epithelium covering the anterior surface of the posterior lobe, that makes pituitrin; after its manufacture it seems to be diffused through the posterior lobe and it is possible that it affects the nervous system and the body as a whole through intermediation of the posterior lobe. If this view be correct then either (1) cessation of manufacture of pituitrin from disease of the pars intermedia or (2) interference with the mechanism through which pituitrin exerts its influence on the nervous sytem (and on the rest of the body) owing to diseases of the pars posterior, might be the cause of a true diabetes insipidus. At present the cost of a pituitrin therapy that has to be kept up a long time is a serious matter. The necessity of administering this hormone hypodermically, rather than by mouth, over a long period is another serious difficulty. Animal experiment indicates that large doses to animals by mouth do have an effect upon the urinary output, so it is conceivable that if pituitrin could be made synthetically, and cheaply; we could give enough of it by the mouth to regulate the urinary concentration satisfactorily. It may be, too, that certain chemical substances known to be closely allied to pituitrin, if not identical with this hormone, namely certain amines, derived in one instance from histidin and, in the other, from phenylalanin and also a substance derivable from ergot, will prove to be efficacious therapeutic agents, suitable to substitute for pituitrin. This whole question of the physiology of the renal secretion and its regulation by products of distant organs is an extremely interesting one; but it would take too long to go further into it at this time.

FURTHER STUDIES IN EXPERIMENTAL ATHEROSCLEROSIS

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Several years ago the writer[1] reported some experiments on dogs as a contribution to the study of experimental atherosclerosis. Since that preliminary report the experiments have been continued, and though much of these very elusive problems is still far from being clear, it is thought best to report some of the results of further study. It may be well to summarize briefly the contents of the article just referred to. Infectious disease has frequently been insisted upon as an important etiological factor in atherosclerosis. In order to test this, dogs were infected with pure cultures of various pathogenic bacteria and also with bacterial toxins by means of injections into the jugular vein. The animals were kept in a state of mild chronic sepsis for periods ranging from four to seven months. The results, so far as the bloodvessels were concerned, were entirely negative. Lead and nicotin also gave negative results. General overexertion maintained by keeping dogs running for many hours daily at top speed, on a specially constructed tread-mill, and continuing this for many months both with and without the hypertension produced by the injection of large doses of adrenalin, also proved without effect. The parenteral methods were then abandoned and feeding experiments were taken up. Some attempts were made with cottonseed oil, which, however, proved too toxic. Then two dogs were fed daily with pure cholesterol in $\frac{1}{2}$-gram doses enclosed in capsules. These two dogs died after one and a half and two and a half months respectively. In the former publication positive results are claimed for these two experiments because a number of whitish-yellow streaks, very slightly raised above the level of

[1] Jour. Exp. Med., 1914, No. 2, xx, 93.

the intima, were found in the aortas. In the light of later experience these can no longer be considered as positive results. The doses of cholesterol were too small; dogs eliminate cholesterol more rapidly and completely than rabbits, and under these conditions one and a half and two and a half months would appear altogether too short a time for the development of so insidious and chronic a lesion as atherosclerosis. Moreover, experience has shown that these insignificant ridges and patches are found fairly regularly in the aorta of young and healthy individuals both canine and human. There will be occasion to speak of this more in detail presently. It is not necessary to recount here all the varieties of experimentation that were attempted. It is important, however, to mention two dogs that received, besides their usual food of bread and meat, dilute hydrochloric acid up to sixty drops daily for two months, respectively three months. Both these dogs showed very definite and unmistakable arteriosclerotic patches in various portions of the aorta, and in the one case especially well marked in the lowest portion of the abdominal aorta. There were no traces of ulceration or calcification. Microscopically these patches showed the typical picture of arteriosclerosis, the details of which need not be gone into except just to mention the fact that cholesterol, in its free state, was abundantly present. That these findings could not be accepted unhesitatingly as proving hydrochloric acid to be an important factor in the etiology of arteriosclerosis is obvious. Two experiments are altogether insufficient to clinch so important a conclusion. The time during which the hydrochloric acid feeding was continued was altogether too short, and more important than everything else, the age of the animals could not be ascertained and both dogs were in all probability rather old. It is easily possible, therefore, that the lesions found were not due to experimentation but were spontaneous, for it can no longer be doubted, though it is perhaps not generally recognized, that arteriosclerosis, closely analogous to the human, occurs spontaneously in old and debilitated dogs. It was necessary, therefore, to continue these acid experiments on a little broader basis.

The writer is still of opinion that if it be possible to produce atherosclerosis analogous to or identical with the human, experimentally and with reasonable certainty, the methods employed

should give positive results not only in rabbits, but with a fair constancy in all animals that are subject to spontaneous or typical senile atherosclerosis. Unfortunately animal pathology has been more or less neglected in this respect, and it is quite possible that when more is known of vascular disease in the animal kingdom more favorable subjects for the experimental study of atherosclerosis will be found. Until then, however, dogs would seem sufficiently well adapted for this class of experiments. They are as omnivorous as the human; the structure of their bloodvessels, especially of the aorta, differs not so very greatly from the structure of human arteries; and while they are subject to pronounced senile atherosclerosis the lesions are not obscured and rendered uncertain by such forms of median necrosis as occur spontaneouly in so large a percentage of rabbits. It is the writer's firm conviction, therefore, that the following conditions should be fulfilled before it can be justly claimed that a genuine atherosclerosis has been artificially produced by experiment. (1) The gross lesions must be closely analogous, if not quite identical in every microscopic detail, with human arteriosclerosis. (2) These positive results must be so constant and regular that it is reasonably to be expected that every experiment will give a positive result, with perhaps only an occasional failure under exceptional conditions. Definite conclusions from apparently positive findings in only one or two animals are not permissible. The number of positive results must be sufficiently large, though an exception here and there may occur. In man also there occur instances, from the celebrated case of Harvey's down to modern times, where persons can live even to extreme old age, apparently immune to arteriosclerosis, their arteries remaining soft and elastic up to their death. (3) In order to avoid the probability of the lesions being due to spontaneous degeneration the experiments should all be done on young animals. It might be objected to this that the youthful organism is perhaps possessed of powers of resistance and repair which are materially diminished or lost in older individuals, and that therefore experiments on very young animals would not be likely to give positive results by the method in question even if it fulfilled all conditions on older individuals. In answer to this it may be said that since it has of late

years been positively demonstrated that very young human individuals, even babies, are subject to unmistakable arteriosclerotic lesions under certain conditions it seems more than probable that the same is true of dogs.

It was now necessary to test the action of acids to better advantage. The acids employed are: (1) Hydrochloric acid to verify if possible the apparently positive result that had been obtained in the two former experiments. (2) Lactic acid, because O. Loeb[1] had claimed positive results with this acid and had developed a rather plausible theory concerning the mechanism of its action. (3) Acetic acid, selected because of its occasional occurrence in certain types of digestive disturbance. Other acids, as for instance butyric, might logically and profitably have also been tested, but for various reasons this could not very conveniently be done.

Hydrochloric Acid. The series includes three dogs. All of them are young. Two males, one female. In every case the ordinary chemically pure hydrochloric acid (specific weight not determined) was used. The initial dose in every instance was ten drops mixed with the food of the animal and increased by five drops every third day. In every case it took some time until the animals became accustomed to this unusual admixture in their diet. They would leave portions of their food, at times would not eat at all; sometimes the dose of acid would have to be diminished; at other times the administration of the acid would have to be stopped altogether for a few days. But after a longer or shorter period the animals became thoroughly habituated to the acid and ate with great appetite while the doses of acid were steadily increased. This is true, it should be said, not only of the hydrochloric acid series but of the two other acids as well. In the hydrochloric set there was one experiment that was rather disappointing. It concerned a

I. Brown male dog. December 5, 1914. Weight 8500 gm. Commenced with 10 drops, increased by 5 drops every third day. Eats well until December 28, by which time he reached 65 drops. Now begins to leave some food and to lose weight.

[1] Ueber experimentelle Arterienveränderungen mit besonderer Berücksichtigung der Wirkung der Milchsaüre auf Grund eigener Versuche, Deutsch. med. Wchnschr., 1913, xxxix, 1819.

December 30. Weight 7600 gm. After a few days of 70 drops he is kept at 60 from January 1, 1915, to February 10. During all this time he eats well but loses weight steadily. Seventy drops up to February 16. Refuses food entirely for two days; dies February 18. Weight at death 5500 gm. Experiment had lasted only about two and one-half months, during which time he took about 250 c.c. of hydrochloric acid. Besides the usual small, punched-out erosions in the stomach and the upper intestine and a great number of round worms there are no definite lesions apparent, except general atrophy and marasmus.

II. Young brindle bull, female. December 1, 1914. Weight 9500 gm. Commenced with 10 drops as usual. After a few days weight begins to decrease. Acid has to be stopped, then again resumed; sometimes the dog eats well, at other times leaves great portions of her food. Weight increases slightly, then is again diminished, the lowest weight being 6800 gm. on March 22. Appetite, however, is excellent and 80 drops of acid are given daily. From now on the dose of acid is increased by 10 drops about every two weeks. Weight increases steadily; the animal is in excellent condition. August 25 the dog gives birth to six healthy puppies. From July 6 to October 19, 1915, when the animal was killed, 140 drops were taken daily. Duration of the experiment ten months seventeen days; total amount of hydrochloric acid consumed somewhat over 2000 c.c. The autopsy shows a very slight hyperemia in scattered areas through the gastro-intestinal tract. Otherwise there is nothing abnormal.

III. Black and white male dog. February 19, 1915. Weight 8700 gm. He is started at once at 40 drops, but though he does not eat well and is losing weight the dose is steadily increased. Weight varies, sometimes more, sometimes less. Though there are times when he absolutely refuses to eat the dose is still increased and he begins to gain steadily in weight. He was killed October 15, when his weight was 9700 gm. From July 30 to death he had taken 140 drops daily, ate all his food, and seemed in excellent health. The experiment had lasted just about eight months, during which time he had consumed a little more than 1600 c.c.

The autopsy showed besides the usual intestinal parasites fairly normal conditions. There was not even any very extensive hyperemia in the stomach and intestines.

Lactic Acid. On the whole it seems that the animals did not take to lactic acid quite as easily as they did to hydrochloric.

I. Young female fox terrier. December 1, 1914. Weight 6000 gm. Commenced with 10 drops daily, and when after a week 20 drops were given the animal refused food and weight decreased very rapidly. December 10 the lactic acid is stopped altogether and on February 16, 1915, weight is about 4800 gm. The animal is kept on normal food without

any acid until June 4. On that day, having been eating well and being in good condition, lactic acid is given again with an initial dose of 90 drops. From now on appetite is excellent and increase in weight steady. The dosage of lactic acid is rapidly increased, and from September 19 until October 14, when the dog is killed, 140 drops are taken daily. Weight at death 11,606 gm. The dog was under observation for ten and one-half months, but the lactic acid experiment counting from June 4, 1915, lasted a little over four months, in which somewhat more than 1000 c.c. were administered. At the autopsy some patchy hyperemia in the gastro-intestinal tract was found, otherwise no organic lesions. No definite macroscopic signs of arteriosclerosis, although the yellowish ridges and patches in the arch and in the descending aorta are a little more pronounced than usual.

II. Male bull terrier. Similar history. December 1, 1915. Weight 13,000 gm. Eating well for several weeks, though weight decreases. Leaves large portion of his food for about a week, then begins to eat well again. Weight varies up and down and appetite varies also. Sometimes the dose of lactic acid had to be diminished; sometimes stopped altogether for a day or two. He had gotten up to 175 drops, then it had to be diminished again to 80. By February 24 he reached his lowest weight 10,300 gm. From now on he increases steadily in weight and eats everything. From June 14 until October 8, when he is killed, he takes 200 drops of lactic acid daily. The experiment lasted about ten months; total amount of lactic acid approximately about 3000 c.c.

At the autopsy no gross lesions of any kind were found.

III. Brown and white female cur. December 29, 1914. Weight 10,700 gm. History very similar to the foregoing. It took until about February 24, 1915, for the animal to become accustomed to the lactic acid. On that day the minimum weight of 6500 gm. was reached, but from now on the dog showed excellent appetite, and ate everything he could get, steadily increasing in weight. From June 4 to October 13, when the dog was killed, he took 160 drops daily, and his weight at death was 12,700 gm. The experiment lasted about nine and one-half months. Total amount of lactic acid consumed was somewhat over 2000 drops. The dog had given birth to a litter of pups two days before death.

Autopsy showed no gross lesions.

Acetic Acid. Again the history is about the same as in the foregoing two series. Fifty per cent. glacial acetic acid CP was used.

I. Male brindle bull. December 29, 1914. Weight 8100 gm. There are the usual variations in weight up to a certain lower limit; dosage of acid is increased or diminished according as the animal takes its food. It takes until about March 9 before the dog is fully accustomed to the acid.

From now on his appetite is excellent, health good, and weight steadily increasing. From June 14 to October 7, when he was killed, the daily dose was 150 drops. Weight on day of death 12,000 gm. Experiment lasted nine months and ten days. Total quantity of glacial acetic acid consumed approximately 2000 c.c.

Autopsy shows no gross lesions.

II. Male coach dog. December 1, 1914. Weight 9700 gm. There are similar variations in weight and in dosage. It takes until February 23 before he gets the habit. From then on the dose of acid and weight are steadily increased, though there are occasional bloody stools. June 1, 1915, he was killed in a fight. Weight at death 10,200 gm. From April 25 to date of death 150 drops of acid daily, with excellent appetite. Experiment lasted six months. Total amount of glacial acetic acid approximately somewhat over 1000 c.c.

Autopsy shows no gross lesions.

It is not necessary to give any details of the microscopic examinations. All that need be said is that no lesion was discovered which could be interpreted as analogous to arteriosclerosis. The positive findings in the two dogs reported by the writer several years ago were therefore evidently not due to the hydrochloric acid, but were spontaneous and probably of the senile type. O. Loeb's claims of positive results with lactic acid are also not convincing. The one dog eight years old Loeb himself throws out on account of his age. In the other dog, only one and a half years old, he regards as arteriosclerotic, having various small ridges and patches in the intima of the aorta. He gives no microscopic details, and it is therefore not at all unlikely that these patches and ridges were no more significant than those found so very frequently in the aorta of normal dogs, both young and old. It can therefore be safely asserted that the feeding of dogs with quite large quantities of various acids for a comparatively long period, though the cause of weeks of severe indigestion and marasmus has not resulted in any lesions comparable to arteriosclerosis.

As cholesterol still appears to occupy the most prominent place in studies on arteriosclerosis it was resolved to revert once more to experiments with that substance. Meanwhile a very interesting paper by Klotz[1] had appeared reporting the effects of injections of cholesterol dissolved in pure oils or as a soap emulsion into the ear

[1] Vascular Changes following Intravenous Injections of Fat and Cholesterin, Jour. Med. Research, November, 1915, No. 2, xxxiii, 157–170.

vein of rabbits. It was decided therefore to try somewhat similar experiments on dogs.

Some attempts were made to develop a technic by means of which cholesterol was to be injected directly into the heart or into the aorta. The only result of these tentative experiments was the production of some very beautiful cases of hemorrhagic and exudative pericarditis. It was then decided to inject cholesterol through the jugular veins. This series includes four dogs. All four were young animals probably barely a year old. The cholesterol was obtained from gall-stones and thoroughly purified, and it was dissolved in sesame oil, which was cheap and practically non-toxic. Its phytesterol content being, as in all similar oils, less than 1 per cent., could in the small quantities used in each injection be considered negligible. It was found that 0.2 cholesterol in about 8 c.c. of sesame oil, at body temperature, gave a perfectly clear solution. This solution was employed exclusively. Any attempt to increase the quantity of oil or use a higher concentration of cholesterol gave rise to more or less grave disturbances, as, for instance, very acute pulmonary edema and speedy death of the animal. For the first few injections ether was given and a very small incision into the skin was made and the jugular laid bare. It soon became evident, however, that the incision was not necessary and that the vein could be reached with absolute certainty, after a little practice, through the intact skin. Still later it appeared that the ether could be dispensed with, for the dogs, willingly and without struggle, permitted themselves to be tied down and did not seem to mind in the least the puncture of the skin and the injection into the vein. Two injections a week were given regularly and without any exception for a period of between eight and nine months. The total amount of cholesterol consumed by each animal during that period was about 11 gm. No deleterious effect of the injection was noticed at any time. It was thought of some interest to observe if a permanent rise in blood-pressure had any effect upon the result of the injections. For this purpose in two of the dogs before any injections were made the abdominal aorta was tied by the Halsted[1]

[1] Partial Occlusion of the Thoracic and Abdominal Aorta by Bands of Fresh Aorta and of Fascia Lata, Proc. Soc. Exp. Biol. and Med., 1913, p. 113.

method. A flap of the fascia lata was taken, with which the aorta was tied somewhat below the right renal artery. The ligature was tightened so that pulsation in the femoral artery could just be felt. In both cases the operations were uneventful and the wound healed without any difficulty, owing no doubt to the skilful manner in which the operations were performed by Dr. M. J. Sittenfield, to whom I feel indebted for his valuable assistance. As the autopsies later on showed, permanent stricture of the aorta was accomplished by this operation. This must necessarily have affected not only the pressure in the aortic system but also, indirectly at least, in the pulmonary circulation into which the cholesterol was primarily discharged.

The further history of these four dogs is rather monotonous. During the very hot and humid summer of 1916 the animals suffered severely from the mange, but with the coming of cool weather and with the necessary dermatological attention they recovered fairly well, and were in good condition when they were killed. One dog did not seem to recover his health entirely after the mange was cured, but continued losing weight and had frequent bloody stools. The injections were, notwithstanding this, continued regularly. November 16 he was in an almost dying condition, and was killed on that day. At the autopsy it was found that the entire intestinal tract, including stomach and colon, showed hemorrhagic swellings with partial destruction of the muscularis. The contents of the intestines were bloody and the mucosa itself was in many places hemorrhagic. There were numerous ulcers, some of them extending down to the serosa. Great numbers of Ascaris mystax were present. In all four dogs the lungs at autopsy were found much firmer than normal, and not completely collapsed. There were also present small wedge-shaped hemorrhagic infarctions and patches of brown pigmentation evidently due to old hemorrhages. Liver, kidneys, and pancreas appeared normal. The adrenals were not enlarged and showed no gross lesions. The spleen in nearly every case was somewhat enlarged and showed very large, prominent follicles. In one case there was some softening of the pulp, probably due to hemorrhage. In one of the cases, where the aorta had been tied, a definite, fairly close stricture of the vessel was seen, surrounded by an area

of thickening, but no noticeable dilatation proximal to the obstruction. In the other operated dog there was also an area of thickening about the place of ligature, but the aorta appeared of practically uniform caliber, possibly very slightly constricted at the place where the ligature had been applied. No gross lesion could be recognized in any of the jugulars, and it may as well be stated here that the microscopic examination also showed perfectly normal conditions, with only here and there a small droplet of fat in the adventitia. Neither the frequent passage of oil and cholesterol through the vein nor its puncture several hundred times by a rather large needle seems to have had an injurious effect upon the delicate vessel. No trace of inflammation or degeneration could be seen. The heart muscle in every instance was flabby, and was found in diastolic dilatation. There was no hypertrophy of the right ventricle. The animals were killed by the injection of chloroform into the jugular vein, and to this the flabby and dilated condition of the heart muscle may be ascribed. The aortas showed some ridges and patches and wrinklings here and there, more frequently around the orifices of branching vessels. These irregularities in the intima of the aorta are usually scarcely visible to the naked eye, especially in the fresh object, unless one has become familiar with them and searches for them carefully. After the artery has been kept in formalin for some time they become a little more distinct. Besides these, however, there were plainly visible more extensive sclerotic thickenings. This was especially the case in one aorta (Fig. 1), in which, in the sinus Valsalvæ behind the semilunar valves, these sclerotic areas protruded more distinctly. In the bulb of this aorta also and near the orifice of the branching intercostal arteries a number of ridges were noticed which tended to confirm the impression of incipient sclerosis.

The oil and cholesterol injected into the jugular is, of course, carried through the upper cava and the right auricle into the right ventricle, and from there through the pulmonary artery into the lungs. It might be confidently expected, therefore, that if any changes in the arteries are to result from this procedure they would show primarily in the pulmonaris rather than in the aorta, for the first powerful impact of the blood laden with cholesterol is directed

against the former. This expectation was completely verified. In all four dogs very definite changes, producing the distinct impression of arteriosclerotic thickening and loss of elasticity, appeared in the pulmonaris (Figs. 1 and 2). There were no signs of ulceration or calcification nor any appreciable dilatation. These departures from the normal were principally of the nodular type, protruding

FIG. 1[1]

more or less prominently into the lumen of the vessel. They commenced immediately behind the valvular cusps, showed the faint whitish-yellow tint common to all sclerotic lesions of the intima, and extended more or less farther up into the vessel. These nodulations were most pronounced in the two dogs in which the aorta had been tied. In the other two dogs the lesions, though quite

[1] Acknowledgment is made to Journal of Experimental Medicine for the loan of illustrations.

definite and plain, were very much less in extent and prominence. It is not possible to say whether this is merely coincidental or whether the increased blood-pressure is somehow responsible. The most marked sclerotic changes were found in the dogs whose aorta showed comparatively slight obstruction. While the gross lesions of the main trunk of the pulmonary artery closely resembled ordinary intimal arteriosclerosis before the development of atheroma has begun, the microscopic examination revealed a condition entirely

Fig. 2

unexpected, and in many ways rather surprising. Hypertrophy of the intima with proliferation of the endothelium, new formation of connective tissue, and the splitting of the elastica interna as described by Jores was distinctly in evidence. This hypertrophy of the intima, however, was comparatively limited and not at all commensurate with the amount of thickening. In many places there was hardly any proliferation of the intima or it was entirely absent. *The most pronounced and constant and evidently primary lesions were found in the media*, and especially in its innermost

portions adjoining the elastica interna. Within this region there had taken place much damage to the elastic tissue. Everywhere the breaking up of elastic fibers into larger and smaller pieces and into granules ("Körnchenzerfall") could be seen. Very often it appeared as if the elastic fibers, especially the larger ones, had suddenly snapped and the ends could be seen some distance apart coiled like the lash of a whip. Evidently secondary to this forcible disruption of the elastic tissue the muscular elements were separated into bundles of varying dimensions and at varying angles, and so pushed aside as to leave wider or narrower gaps between them; and there seems to be no doubt that this disorganization of the elements of the media was largely responsible for the prominent areas of apparent thickening and that the proliferation of the intima took only a minor and secondary part in the process (Fig. 3). These comparatively wide gaps between the dislocated groups of muscle cells usually contained remnants of broken-up elastic fibers, but otherwise appeared empty (Fig. 4). That they were not empty could be surmised from the compactness and solidity of the nodules. Edema could be positively excluded; staining for fibrin or mucin gave no results; but with certain stains, as, for example, alumcarmin, the faintest possible tinge could be obtained, sometimes showing slight inequalities and suggesting some very delicate coagulated material. It is probable that these wide areas contain, as Ribbert[1] suggested, coagulated blood plasma. He finds these gaps, however, only in the intima, where he believes they are the effect of excessively high blood-pressure, to which also he attributes the deposit of cholesterol. Not the slightest sign of necrosis could be detected, and there was nothing to remind one of the median necrosis as seen in rabbits or in human arteries. The muscle cells, although detached from their normal position, were in perfect condition, and the elastic fibers, though shattered and disorganized, retained their normal staining properties. There were no inflammatory symptoms and the vasa vasorum were normal. It seemed clear that the entire process was purely mechanical. The sclerotic areas in the aorta showed the same median disorganization even more strictly confined to the media, for the intima was mostly not affected but normal.

[1] Ueber die Genese der arteriosklerotischen Veränderungen der Intima, Verhandlungen der. Deutsch. path. Gesellschaft., 1905, p. 169.

The lungs presented a very constant and characteristic microscopic picture. Even a very superficial examination showed that the bulk of the oil and its cholesterol content was filtered out

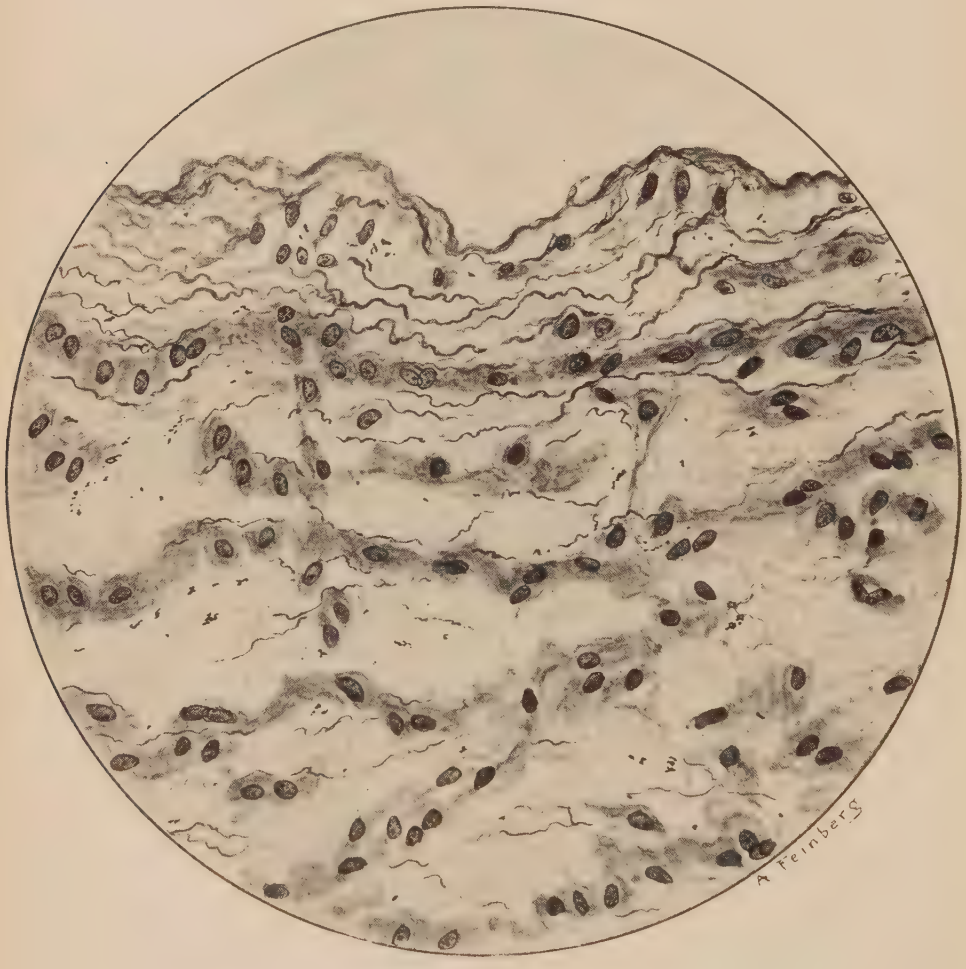

Fig. 3

through these organs. The sudanophile masses were deposited almost exclusively in the interalveolar septi, and there mainly in the capillaries. These were much distended and filled to bursting

with oil. Very frequently the distended capillaries were surrounded by an infiltration of leukocytes, both processes together causing a considerable thickening of the septi with very marked encroachment

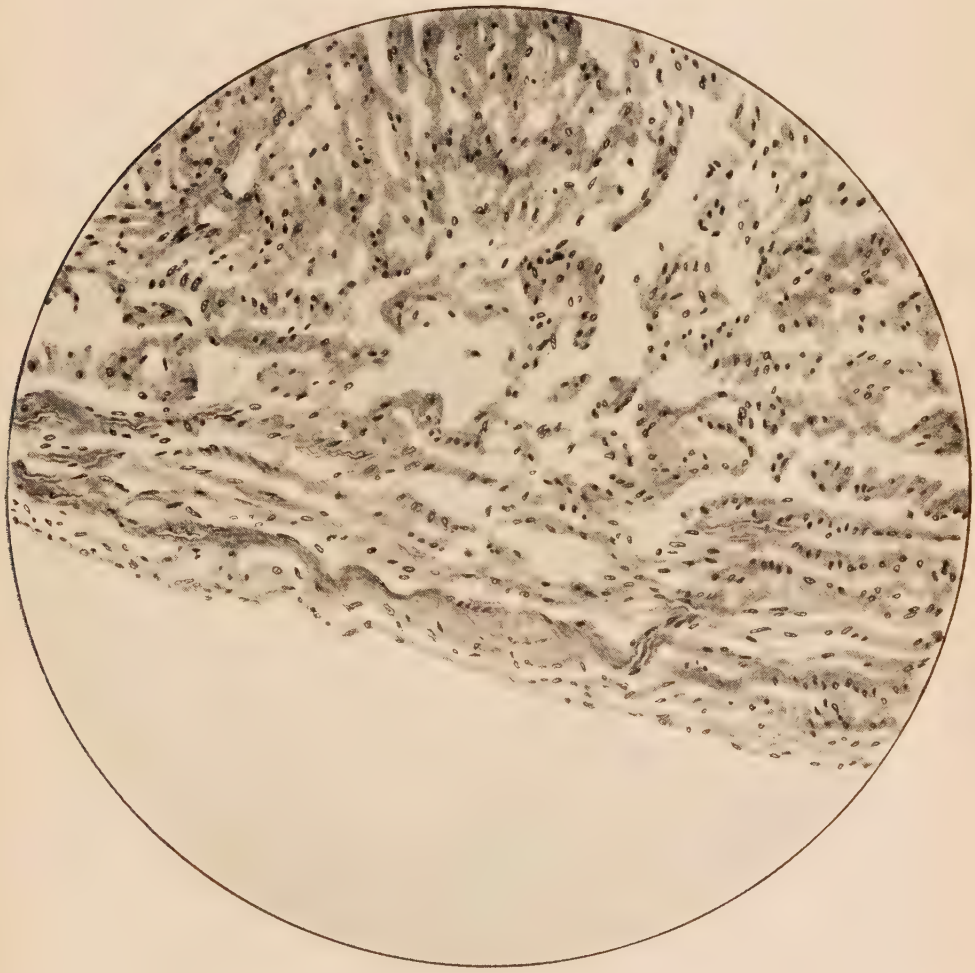

Fig. 4

upon the alveolar air spaces. The alveoli themselves were practically free from oil. Here and there an overdistended capillary would burst and a few drops of oil be left in the alveoli. Dispersed through-

out the lung there were clear indications of hemorrhages. Numerous red blood corpuscles were found here and there in the air spaces and in the septi, and hemorrhagic infarctions were also irregularly scattered throughout the lungs, especially near the margins. Notwithstanding all this the pulmonary apparatus seemed quite adequate to combat the enormous overburdening caused by the oil injections. Clinically there were no symptoms of respiratory disturbance, and this could be accounted for by the fact that though the pulmonary circulation was heavily overtaxed, nevertheless capillaries and alveoli always remained unaffected in sufficient numbers to ensure the necessary aeration of the blood. There is, moreover, good reason to believe that the oil was very rapidly discharged from the lung. If the dog was killed within twenty-four hours of an oil injection the lungs were found overcrowded with sudanophile masses, while if two or three days had elapsed between the injection and the killing, comparatively but very little of sudanophile material remained and the lungs presented an appearance more nearly approaching the normal. It appears that there is a very marked difference between the reaction to cholesterol in oil as shown in the lungs of the dog compared to that described by Klotz[1] in the rabbit's lung. A very careful study of a large number of sections of the lungs of all the dogs and from all parts of the lung failed to show any crystals or any doubly refracting substances. Phagocytes with granular fatty inclusions were scattered throughout the lungs, mostly in the septi, occasionally in the alvoli. Extensive areas of the lung, however, appeared free from phagocytes. On the other hand, it is the writer's impression, though he cannot speak with absolute certainty, that in certain localities, often near the margins, or where the pulmonary tissues had become more or less indurated by hemorrhagic infarctions and the subsequent reactive processes, and where accordingly the circulation was materially interfered with and the bloodvessels were presumably no longer able to carry off the fatty material with sufficient dispatch, that in such territories the phagocytes accumulated in considerable numbers, presumably to replace or rather materially to aid the work of the bloodvessels. In such

[1] Loc. cit.

spots large phagocytic cells filled with granular sudanophile material are heaped in close proximity. Very frequently several of these cells merge into one large giant cell, the several nuclei being distributed irregularly, some in the center and others pushed aside toward the circumference. Many large cells filled with granules of brown or blackish pigment and resembling very closely the "Herzfehlerzellen" are also found in these indurated areas. The bloodvessels in the dog's lung also showed somewhat different reactions from those described by Klotz for the rabbit. The pulmonary veins as well as the bronchial arteries appeared to be perfectly normal. The capillaries also, notwithstanding the tremendous strain to which they were subjected by the overcrowding with oil, did not show any structural lesions. The smaller and smallest branches of the pulmonary artery were also without exception perfectly normal. It was only in the right and left main branches of the pulmonary trunk and their subdivisions of the second and third order that very definite structural changes in the vascular walls were found. It was impossible to decide if there was any dilatation of these larger vessels, as there were no normal measurements available that might have served as a standard; but the general impression was that if any dilatation had actually taken place it could not be very serious. Several small globular nodules were found in the two main branches, though they were not as large nor as extensive as those described in the main trunk. The microscope showed that these little globules were the result of a very marked and peculiar hyperplasia of the media. The elastic lamelli and the muscle fibers were not arranged in the usual symmetrical layers but formed more or less irregular concentric circles or in other places abutted upon each other at various angles, thus producing upon the whole the impression of a whorl of tissue. Within these peculiar nodulations the elastic fibers have also here and there given way and snapped asunder, and here also spaces apparently filled with plasma and containing remnants of broken elastic tissue occur. The dislocation and forcing apart of the elements of the media and the destruction of elastic tissue is, however, minimal when compared with these same processes as seen in the main trunk. Another peculiarity of this strange form of nodulation

FIG. 5

is that it is practically impossible to decide where the media ends or the intima begins. No elastica interna is visible and the innermost layers of the vessel consist of fibrous and muscular tissue, all included in a fine network of delicate elastic fibers forming irregular meshes, and the whole is lined with moderately proliferating endothelium. Rather small phagocytes are occasionally, but on the whole very rarely, to be found, as also very minute sudanophile droplets between the cells. Very definite and typical hyperplasia of the intima, independent of those hypertrophic median nodules, are also found in the two main branches, but especially in some of the larger arteries well within the lungs (Fig. 5). Here there is comparatively little change in the condition of the media, although very small spaces filled with plasma and containing fragments of elastic fibers are sometimes seen just below the elastica interna. These thickenings of the intima, though they distort the lumen of the vessel but very slightly, agree very accurately with the description given by Jores.[1] There is the splitting of the elastica interna, the new formation of fibrous and muscle cells, and some proliferation of the endothelium; but there is this difference, that there is no pronounced fat phanerosis or fatty degeneration. It is true that some fat phagocytes and minute fatty droplets are found in the intima and even sometimes in the inner layers of the media, but they are few in number and not at all constant in occurrence nor regular in distribution.

It is obvious therefore that though the pulmonary circulation was for many months overcrowded with cholesterol in oil; though there must have existed a certain amount of hypercholesterinemia, as witness the excess of sudanophile bodies appearing throughout the heart muscle, the liver, spleen, kidneys, and adrenals; and though the pressure within the pulmonary, and also, though perhaps to a lesser degree, in the aortic system, must have been very great, the cholesterol evidently took no essential part in the processes that led to such profound changes in the structure of the arterial walls.

What relations, if any, do these findings bear to human atherosclerosis? It is now very generally believed that the latter is an

[1] Wesen und Entwickelung der Arteriosklerose, 1903.

affection primarily of the intima, essentially degenerative in character, and that cholesterol and its esters are very important factors in this process. The results of the present experiments, on the other hand, are apparently in direct opposition to this theory. Though to the naked eye the nodules protruding into the lumen of the vessels, and also the occasional diffuse thickening of the vascular walls, closely resemble arteriosclerosis at a stage in which ulceration and calcification have not as yet begun, the real localization of the lesion is found to be mainly in the media. The structural disruptions and dislocations appear to be the result of the action of mechanical forces rather than of chemical degenerative reactions. The hypertrophy or hyperplasia of the intima is obviously merely secondary to the lesions in the media, and lastly it would appear that cholesterol does not count as a factor in the process. Notwithstanding these seemingly important differences the present writer is nevertheless of the opinion that a very close analogy, if not identity, exists between human atherosclerosis of the pulmonary bloodvessels and the lesions produced experimentally in our dogs. Our knowledge of human atherosclerosis is as yet far from complete. The controversy between those that assume a mechanical disturbance as primarily the cause of arteriosclerosis; those, on the other hand, that are more inclined to make toxic and other chemical influences responsible; and a third party, pursuing a middle course, and seek to explain the sclerotic phenomena by combining in various ways the extreme views of both sides, is still unsettled. Aside from the problems of atherosclerosis in general, however, what is known of sclerosis of the pulmonary system must be taken especially into account. It is not so very many years ago that it was supposed that sclerosis of the pulmonary artery, if it occurred at all, was extremely rare. Bichat[1] seeks to show that vessels carrying venous blood seldom if ever show traces of sclerosis, and hence, according to him, the pulmonary artery in which only venous blood circulates is practically exempt. Since about the last twelve to fifteen years the subject has been more intensely studied and quite

[1] Quoted by Brüning: Untersuchungen über das Vorkommen der Angiosklerose im Lungenkreislauf, Ziegler's Beiträge, 1901, p. 457.

a literature has grown up around it. It is beyond the scope of this paper to go into literary details. A very complete review of the literature on this subject may be found in Posselt[1] and more recently in Ljungdahl.[2]

It is fairly certain now that pulmonary sclerosis is found quite frequently if it is only carefully looked for. Genuine senile sclerosis of the pulmonary artery seems to be quite rare, but according to Ljungdahl, contrary to the view of many authors, it does occur, but mainly in association with special complications, pulmonary emphysema for instance, that tend to raise the pressure within the artery very considerably. Walther Fischer[3] found in several cases of advanced atherosclerosis of the aorta and peripheral arteries the pulmonary arteries quite healthy; but in these cases the lungs were free from emphysema or other chronic lesions and there was no hypertrophy of the right heart. Posselt finds that sclerosis of the pulmonary artery seems to affect youthful persons more readily than is the rule in sclerosis of the aortic vessels. According to this author 97 out of 187 cases were found in individuals under forty, 125 in subjects under fifty, and only 60 in persons above fifty years of age. All authors, however, seem agreed that hypertension within the pulmonary circulation is a main factor in the etiology of sclerosis of the pulmonary artery, which is generally looked upon as an Abnutzungskranheit as defined by Marchand. The fact frequently observed, that the artery remains intact though the blood-pressure is steadily much above normal, strongly suggests that hypertension is not the only factor, but that other etiological elements, such as local or functional variations, toxic or other influences as yet unknown, are also involved. For the pulmonary artery, too, the dogma that the intima is the primary seat of the pathological changes is very generally accepted. There are, however, some dissenting voices. Ehlers[4] finds that the human pulmonary

[1] Die Erkrankungen der Lungenschlagader, Lubarsch u. Ostertag Ergebnisse, I. Abteilung, 1909, p. 298 ff.

[2] Untersuchungen über die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, 1915.

[3] Ueber die Sklerose der Lungenarterien und ihre Entstehung., Deutsch. Arch. f. klin. Med., 1909, xcvii, 230.

[4] Zur Histologie der Arteriosklerose der Pulmonalarterie, Virchows Arch., 1904, Bd. 178, S. 427.

artery differs from the aorta in that its media is made up of two distinct layers, and according to him the innermost layer assumes a very active part in pathological processes. Durante[1] reports a case of congenital atheroma in a premature infant. He finds the vasa vasorum normal, the intima mostly normal. The main process is in the inner third of the media, where there is some necrosis and calcification. He also describes broad, almost unstainable gaps in the media. There is some secondary hypertrophy of the intima, but only over points of most advanced degeneration of the media. The aorta appears macroscopically normal, but under the microscope it is seen that in its media there are similar processes developing as in the pulmonary. Except for the median necrosis and calcification the conditions in this case seem to bear a striking resemblance to those obtained experimentally in our dogs.

These few brief notes from the literature will suffice to show that the results of the experiments here described present some very obvious analogies to the sclerosis of the human pulmonary artery, but at the same time some very distinct differences. The proliferation of the intima wherever it is found is the exact counterpart of what is considered typical for human atherosclerosis, and in the section taken from a branch within the lung and in which the media is barely affected (Fig. 5), the picture is identical with any that can be taken from an arteriosclerotic artery that has not as yet undergone an appreciable amount of degeneration. One of the principal points of difference is that in our dogs it is not the intima but the media which is without doubt the primary and principal localization of the lesion. That this is not necessarily peculiar to the dog but can be found also in human pulmonary arteries is sufficiently proved by the above quotations from Ehlers and Durante. Perhaps greater experience and improved methods may bring forward a greater number of similar human cases. Our experiments, moreover, have shown the process at a much earlier stage than it is likely to be frequently seen in the human. That the peculiar structure of the pulmonary artery as described by Ehlers is not to be held responsible for this localization in the media is obvious, because identical

[1] Athérome congénital de l'aorte et de l'artère pulmonaire, Bull. Soc. anat. de Paris, 1890, lxxiv, 97.

lesions may be found at the same time in the aorta. One is apt therefore to recur to the original theory of Thoma,[1] who assumed some defect in structure or in function of the media as the initial stage in the development of atherosclerosis. The almost uncomplicated hyperplasia of the intima as seen in some of the larger arteries within the lung itself might also be readily accounted for by the early theories of Thoma. These arteries are without doubt dilating under pressure, the current is probably considerably slower than normal, and hence the compensatory thickening of the intima. It might be assumed that the effect upon the media was comparatively slight, because in arteries of that order the muscular apparatus is not sufficiently developed to exert any great resistance to the pressure within the artery. The disorganization in varying degree of elastic lamelli and fibers is admitted by all observers, but is generally conceived as taking place principally in the intima, and only to a very limited extent in the media. It is taken to be a direct consequence of fatty degeneration. According to Torhorst[2] degeneration does not commence before the completion of the hyperplastic process in the intima, and he as well as most other investigators, especially Aschoff,[3] see the cause of the breaking up of the elastic elements in the fatty degeneration of the cement ("Kittsubstanz") that serves to hold the fibers together. In the present set of experiments not the slightest trace of degeneration, fatty or otherwise, could be found. The violent destruction of the elastic elements, the forcible displacement of the muscle cells, the broad gaps filled with plasma, all point to a purely mechanical force, in all probability the intense straining of the musculature of the arteries to overcome the resistance offered by the extensive blocking of the pulmonary circulation in the lung. It will be of great interest to observe if the cholesterol injections, possibly with some modifications, and continued during a much longer period, will eventually lead to fatty degeneration and calcification, though Ljungdahl seems to believe that seven or eight months of increased resistance on the

[1] Ueber die Histomechanik des Gefässsystems und die Pathogenese der Angiosklerose, Virchows Arch., 1911, Bd. cciv, p. 1.

[2] Die Histologischen Veränderungen bei der Sklerose der Pulmonalarterie, Ziegler's Beiträge, 1904, Bd. xxxvi, p. 210.

[3] Arteriosklerose, Beihefte zur med. Klin., 1914, Heft 1.

part of the lungs and increased pressure from the right heart is a sufficiently long time to permit degenerative changes to develop in human pulmonary arteries.

One would think that if cholesterol or its esters participate actively in causing sclerotic lesions such activity would be plainly demonstrated by the present experiments. That cholesterol is practically inert, that no esters, at least no doubly refracting bodies, have been met with, appears to be one of the striking differences between the arterial lesions of our dogs and human atherosclerosis. This discrepancy is, however, not as great as it would seem. The modern trend of opinion, as especially represented by Aschoff, seems to be that deposits of cholesterin esters are secondary to the mechanical conditions by means of which the intima and perhaps also the media undergoes serious structural alterations. Plasma is forced into the intima and the amount of lipoid deposit that takes place depends largely on the cholesterinester content of that plasma. With this precipitation of lipoids degeneration begins, the "Kittsubstnz" is demolished, and those processes initiated that lead to atheroma. This conception is, however, not as yet a well-grounded fact, but rather an hypothesis. It is true that cholesterol and its esters are invariably found in every case of human atheroma, and that the extent of the degeneration is approximately proportionate to the quantity of lipoids accumulated within the vascular tissues; but up to date nothing very definite is as yet known about the exact conditions that induce the lipoid deposits, nor of the specific functions of the latter. Perhaps there may be some truth in the theories propounded by Lemoine and Gérard,[1] according to which the cholesterol acts as an antitoxin and is heaped up in the degenerating vascular tissues in order to neutralize, and to assist in transporting, the toxic material injected into the bloodvessels by the various processes and diseases that are supposed to lead to arteriosclerosis. In this connection it is very significant that Klotz[2] finds that the hemolytic properties of sodium oleate are neutralized by an adequate admixture of cholesterol. Some added interest as regards the func-

[1] Nature de l'athérome et Role de la cholestérine dans sa formation, Revue mod. de méd. et de Chir., October, 1913, p. 380.

[2] Loc. cit.

tion of cholesterol in arteriosclerosis may also be found in recent studies of sclerotic lesions as found in very young persons and babies, especially by Stumpf[1] and Saltykow.[2] The present writer has also examined a relatively large number of infantile aortas, of several fetuses, and also of dogs. He hopes to publish his results in the near future, but so much can be said now that in the majority of the baby aortas, no matter what the cause of death, no matter how old or how young the child, minute ridges and patches slightly elevated above the level of the intima, and of a faint yellowish color, could be found. They were most frequently found in the sinus Valsalvæ, the bulb or the arch, but often enough in the descending and abdominal aorta and usually in the neighborhood of the orifices of branching vessels. Under the microscope there could regularly be seen a beautifully distinct and typical hyperplasia of the intima, a practically intact media, and here and there very minute sudanophile droplets in the interstices between the elements of the intima, and also fairly large phagocytes filled with sudanophile granules. The same phenomena could with great constancy be found also in the aorta of young dogs. In these cases there were no signs of degeneration, not did there appear to be any tendency toward atheroma, and it must be a subject for further study to ascertain the functions of the cholesterol, and for what reason, and by what mechanism, a baby one day old or a seven months' fetus had small areas of hyperplastic intima and sudanophile phagocytes in its aorta. It seems very probable that the distribution and the presumptive action of cholesterol in these cases and that found in the pulmonary arteries of our dogs is very similar.

As a result of this brief discussion it is believed that the arterial lesions experimentally obtained in our dogs are essentially identical with those found in the human pulmonary artery, and that for the first time atherosclerosis, very closely analogous to the human, has with certainty been produced experimentally in dogs.

SUMMARY. Cholesterol dissolved in sesame oil and injected regularly for a period of from seven to eight months into the jugular

[1] Ueber die Entartungsvorgänge in der Aorta des Kindes und ihre Beziehungen zur Atherosklerose, Ziegler's Beiträge, 1914, lix, 390.

[2] Jugendliche und beginnende Atherosklerose, Korrespondenzbl. f. schweizer Aerzte, 1915, Nr. 34 u. 35.

vein of four young dogs has caused in each animal larger and smaller nodules protruding to some degree into the lumen of the pulmonary artery and also here and there some diffuse thickenings, the whole closely resembling human arteriosclerosis. These changes commence at the origin of the pulmonary artery immediately behind the semilunar valves. They seem a little more pronounced in those dogs that had the aorta tied. Microscopically the lesions are seen to be primary in the media. They consist of a more or less violent disorganization of the elastic elements and displacement of the muscular tissue. As a consequence wide gaps, apparently filled with plasma, are formed in the media. The entire process is localized principally in the inner third of the media. There is no evidence of fatty degeneration either in the elastic elements or the muscle. Typical sclerotic hyperplasia of the intima is found over some of the prominent median nodulations while over others the intima is normal. Hyperplastic sclerosis of the intima is also found in places where the media is intact or only slightly damaged. Some of the larger branches of the pulmonary artery well within the lung tissue are somewhat dilated and show extensive hyperplasia of the intima over almost normal media. Peculiar small nodules are seen in the media of the two main branches of the pulmonary artery, which are found to consist of pure hyperplasia of the elastic and muscular elements arranged in more or less regular concentric circles. The capillaries and smaller and smallest arteries within the lungs are not affected. Cholesterol in phagocytes and in droplets between the tissue elements is present in very small quantities and does not take any active part in the process. The entire process represents in all probability an early stage of arteriosclerosis, a result of purely mechanical stress brought about by the very extensive but more or less intermittent blocking of the pulmonary circulation by the oil. The musculature of the artery appears to be the main force applied to overcome the resistance in the circulation. In no case has hypertrophy of the right heart been found. The lesions in the pulmonary arteries of the dogs produced experimentally are closely analogous to atherosclerosis of the human pulmonary artery.

THE ELABORATION OF SPECIFIC SOLUBLE SUBSTANCE BY PNEUMOCOCCUS DURING GROWTH[1]

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From the study of bacterial infections in man and the lower animals evidence has been accumulated that pathogenic organisms do not produce harmful effects from their mere physical presence. The general reaction or toxemia of infection is differentiated from the local process which in many instances is the only tangible expression of bacterial invasion. Substances of a harmful nature seem to pass out from the bacteria and through the circulating medium of the animal to injure cells and organs at a distance from the site of infection. An explanation of the nature and mode of action of these substances has been one of the great problems in the study of infection. Certain bacteria, such as diphtheria, tetanus, and others, when grown in artificial media form a soluble toxin whose action when injected into animals differs in no way from that manifested when the same bacteria grow in living tissue. The majority of pathogenic bacteria are not known to form these soluble toxins during their life processes. The capacity of the latter to intoxicate has been explained by their setting free upon death a toxin which during life is retained within the cell body. Some investigators hold the view that intoxication by these bacteria arises in the body of the infected animal from the splitting of the

[1] Read before the Association under the title Studies on a Soluble Substance of Bacterial Origin Produced by Pneumococcus.

bacterial protein into toxic degradation products. These explanations of bacterial intoxication are not so satisfactory nor so well substantiated as are the facts concerning infection with bacteria which produce known soluble toxins.

Pneumococcus is a highly pathogenic microörganism which is not known to secrete a soluble toxin, and whose harmful effects are supposed to be due either to the setting free of intracellular toxins or to the formation on disintegration of toxic split products. In the present paper it is shown that this organism during the early stages of its growth forms a readily soluble substance which diffuses into the culture medium *in vitro*, and in human and animal infections is present in the circulating blood, whence it passes through the kidneys into the urine. We have not as yet been able to demonstrate with certainty that this substance is responsible for the intoxication that accompanies lobar pneumonia.

Formation of a Soluble Substance in Culture Media. In 1897 Kraus[1] demonstrated for the first time the presence of specific precipitable substances in the germ-free culture filtrates of certain bacterial species. This work was subsequently extended by other observers, so that it is now known that a large number of bacteria give rise to these substances in the media in which they grow. The precipitin reaction obtained with these substances is strictly specific and occurs only when an homologous immune serum is used. These culture fluids have been studied after the bacteria have grown in them for twenty-four hours or more and their presence has been supposed to be due to the passing into solution of the bacterial substance upon disintegration of the cells. The same precipitable substances may be demonstrated in the bacteria-free salt solution or distilled water extracts of organisms grown on solid media.

Neufeld[2] has shown that solutions of pneumococcus obtained by the addition of small amounts of bile to bouillon cultures produce a specific precipitate in the presence of immune rabbit serum. Wadsworth[3] has obtained similar results not only with bile solutions but also with filtered salt solution extracts of pneumococcus.

[1] Wien. klin. Wchnschr., 1897, x, 736
[2] Ztschr. Hyg. u. Infectionskrankh., 1902, xl, 54.
[3] Jour. Med. Research, 1903–04, x, 228.

Panichi[1] demonstrated the presence of a specific precipitable substance in the filtrate of bouillon cultures of pneumococcus.

The fact which we wish to emphasize in this study is that pneumococcus from the time it starts to grow elaborates in the medium of its environment a specific substance of bacterial origin in considerable amounts and that the early presence of this soluble substance is not attributable to the death and subsequent disintegration of the bacterial cell, but represents the extrusion into the medium of bacterial substance during the life processes of the organism.

TABLE I

Rate of Growth of Culture

Number of hours.	Colonies per c.c.
0	810,000
2	1,170,000
4	26,000,000
6	245,000,000
8	297,000,000
12	382,000,000
24	No growth from 0.0001 c.c.
48	" " " 0.1 c.c.

Titration of Precipitin Reaction in Culture Fluid

Dilution.	After 0 hours.	After 2 hours.	After 4 hours.	After 6 hours.	After 8 hours.	After 12 hours.	After 24 hours.	After 48 hours.
1:1	−[2]	±	+++					
1:5	−	−	++					
1:10	−	−	±	+++	+++	+++	+++	+++
1:15	−	−	±	+++	+++	+++	+++	+++
1:20	−	−	±	+++	+++	+++	+++	+++
1:25	−	−	±	++	++	+++	+++	+++
1:30	−	−	±	+	++	++	+++	++
1:40	−	−	−	+	+	++	++	+
1:50	−	−	−	±	+	+	+	+
1:60	−	−	−	±	±	±	±	±
1:80	−	−	−	±	±	±	±	±
1:100	−	−	−	−	−	±	±	±
1:120	−	−	−	−	−	±	±	±
1:160	−	−	−	−	−	−	−	±
1:200	−	−	−	−	−	−	−	±
1:240	−	−	−	−	−	−	−	±
Control.	−	−	−	−	−	−	−	−

[1] Centralbl. Bakteriol., 1te Abt., Orig., 1907, xliii, 188.

[2] − indicates no reaction; ±, faint trace; +, visible precipitation; ++, flocculation; +++, heavy flocculation.

In the following experiment a flask of bouillon was incubated with a small amount of an early, rapidly growing culture of pneumococcus. A young culture was chosen in order to avoid the occurrence of bacterial lag, during which some cell death occurs. At varying intervals during the growth of the culture, fractions were withdrawn from the flask, freed from bacteria, and the cell-free fluid was tested for the presence of precipitable substances. A bacterial count was made of each specimen in order to determine that the culture was growing at a maximum rate and that little or no cell disintegration had occurred at the time when this substance was already present in considerable amounts. The quantity of precipitable substance present in a given specimen was determined by ascertaining the maximum dilution of the cell-free fluid at which precipitation occurred on the addition of homologous antipneumococcus serum.

A protocol in which Type III pneumococcus was studied is given, since this organism forms a large amount of soluble substance, whereas Type II and Type I form lesser amounts in the order named.

The bacterial counts in the experiment given (Table I) show that the cultures grew at a maximum rate for about twelve hours. Chesney[1] has shown in an elaborate study that during this period the bacteria increase in geometric progression and that the curve of generation time may be plotted as an ascending straight line. From this the deduction may be drawn that during the first twelve hours little or no cell death occurs. Examination of the precipitin reaction with the bacteria-free filtrates of specimens removed from the culture during the first twelve hours of growth reveals the fact that the bacterial substance passes into solution in the culture medium in easily demonstrable amounts during this time. This would seem to indicate that this soluble substance is not the result of bacterial disintegration but represents an actual extrusion of the cell substance into the medium during the life processes of the organism.

Presence of Soluble Substance Derived from Pneumococcus in the Blood and Urine of Infected Rabbits. The

[1] Jour. Exp. Med., 1916, xxiv, 387.

demonstration that pneumococcus during its growth in fluid media gives rise to a soluble substance suggested the likelihood that the same substance might be detected in the body fluids of experimentally infected animals. In order to test this assumption, a rabbit was injected intraperitoneally with 1 c.c. of the blood of a rabbit infected with pneumococcus. At varying intervals after infection specimens of blood were collected from the heart, and the serum, freed from cells, was passed through a Berkefeld filter in order to remove the organisms that had reached the blood stream. The bacteria-free serum was then tested for the presence of precipitable substances by the addition of homologous immune serum. The urine of these rabbits was also tested to find out whether the soluble bacterial substance passed through the kidneys and could be demonstrated by the precipitin reaction in the animal's urine. In Table II an example is given in which the rabbit had been infected with a Type II pneumococcus.

TABLE II

Pneumococcus Precipitin Reaction in the Blood Serum of a Rabbit Infected with Pneumococcus Type II

Time.	Before infection.		2 hrs. after infection.		4 hrs. after infection.		6 hrs. after infection.		8 hrs. after infection.	
Type serum . . .	I	II	I	II	I	II	I	II	I	II
Result	−[1]	−	−	±	−	+±	−	++	−	++

Tests of rabbit urine cannot be made at regular intervals because of the failure of the animal to void frequently. Specimens at the end of twenty-four hours, however, showed a marked precipitate when mixed with the serum corresponding in type with the organism with which the animal was infected.

The experiment given in Table II demonstrates the fact that within a short period of time after intraperitoneal injection of a rabbit with pneumococcus there is present in the filtered blood serum a specifically reacting bacterial substance of pneumococcic

[1] − indicates negative; ±, faint trace; ++, marked flocculation.

origin. This substance readily passes from the blood through the kidneys into the urine and can there be demonstrated in considerable concentration.

PRESENCE OF SOLUBLE SUBSTANCE DERIVED FROM PNEUMOCOCCUS IN THE BLOOD AND URINE OF PATIENTS SUFFERING FROM LOBAR PNEUMONIA. The fact that the pneumococcus forms a readily soluble substance during growth in artificial media and in the body fluids of animals experimentally infected makes it not unreasonable to assume that the same substance is formed by pneumococcus during the course of natural infection in human beings. In order to find out whether or not this is so, the blood sera and urine of a large number of patients suffering from pneumonia due to pneumococcus of Types I, II and III were studied for the presence of this soluble material. Specimens of serum were obtained at varying intervals during the disease and the urine was examined frequently throughout the course of the infection and during convalescence. If the precipitin reaction was not positive with the whole urine, a method of concentrating the urine was employed. It has been found that the soluble substance to which the pneumococcus gives rise is precipitated by alcohol and after precipitation is again readily soluble in water. In order to concentrate the precipitable substance in urine to 25 c.c. or more of the twenty-four-hour specimen a few drops of acetic acid are added and the urine is then boiled down to a volume of 5 c.c., filtered through paper to remove any precipitate of albumin that may occur, and the filtrate added to eight to ten volumes of 95 per cent. alcohol. The precipitate which forms is collected by centrifugalization and dried to remove the excess of alcohol and the residue extracted with 2 or 3 c.c. of salt solution which redissolves the specific substance. Any insoluble material is removed by centrifuging and the clear salt solution extract used in the precipitin test.

In Table III are presented the studies on the presence of the specifically precipitable substance in the blood serum during life of a number of patients suffering from lobar pneumonia. Almost all the patients studied showed a strongly positive precipitin reaction in the urine and were chosen for the purpose of finding out

whether at a time when the substance was being excreted in largest amounts it could also be demonstrated in the circulating blood.

TABLE III

Pneumococcus Precipitin Reaction in the Blood Serum during Lobar Pneumonia

Case No.	Blood test.		Blood culture.	Urine.	Serum treatment.	Result of disease.	Remarks.
	Day of disease.	Result.					
Pneumococcus Type I infection							
2821	6	−	−	++	+	Recovered	Total, 10 cases; 2 died.
2816	8, 9, 10, 11, 12	−	+	++	+	Died	
2901	5, 7, 9	−	+	++	+	"	
2968	6, 7	−	+	+	+	Recovered	
2936	7, 9	−	−	±	+	"	
2815	4	−	−	+	+	"	
2824	3	−	−	±	+	"	
2883	5, 6, 7	−	−	−	+	"	
2858	3, 4, 5	−	−	+	+	"	
2891	3	−	−	+	+	"	
Pneumococcus Type II infection							
2885	3, 4, 6	−	−	+	+	Recovered	
2845	6	++	+	++	+	Died	
2868	4	−	−	−	−	Recovered	
	7			+			
2829	1	−	−	−	−	"	
2879	2	−	+	−	+	"	
	7			+			
2892	5, 6	+	+	++	−	Died	
2834	6, 7, 9, 10, 11	−	+	++	+	"	
2922	4, 5, 6	−	−3	+	+	Recovered	
			+7				
3006	2, 3	−	−	++	−	Died	Blood culture positive on sixth day.
3031	3, 5, 7	+	+	++	+	"	
2869	3, 4, 5	+	±	+	+	"	
Pneumococcus Type III infection							
2898	5, 6, 7	++	+	++	−	Died	Total, 4 cases.
2947	6, 10, 11	±	−	+	−	Recovered	
2797		+	−	+	−	Died	
2783	7	+	+	+	−	"	

In all, 25 cases were examined, of which 10 were due to infection with Type I pneumococcus, 11 with Type II, and 4 with Type III. Of the Type I infections, none gave a positive precipitin reaction

in the serum, although in all but one the urine was positive at the time the tests were made and in three instances the reaction in the urine was heavy, indicating the excretion of the soluble substance in considerable quantity. The failure to demonstrate the substance in blood in Type I pneumonias may be partly attributable to the fact that all these cases were treated with Type I antipneumococcus serum, which is known to cause the disappearance of the substance from the urine in many cases during treatment. It has also been shown by *in vitro* experiments that Pneumococcus Type I forms less of the soluble substance than organisms of Types II and III. The sera of 11 cases of Type II pneumonia were studied. The urine reaction was positive in 10 of these, while the precipitin reaction in the blood was positive in 4 instances. Of these 11 cases 7 were treated with Type II serum. Among the 7 serum-treated cases, 3 showed a positive precipitin reaction in the blood. Of the 4 cases not treated with serum, only 1 gave a positive blood test. A positive blood culture was obtained in 7 of the 11 cases studied. Of the 4 cases with a positive precipitin test in the serum, all showed a positive blood culture, while of the 7 cases with a negative precipitin test in the serum, 3 had a positive blood culture. All 4 patients showing a positive precipitin reaction in the blood serum died, whereas of the 7 with a negative serum test, 2 died and 5 recovered.

Four cases of pneumonia due to Pneumococcus Type III were studied. All gave a positive precipitin test in the blood serum. Blood cultures were positive in two instances and the precipitin reaction in the urine was positive in all. The infection was fatal in 3 of the 4 patients.

In Table IV are presented the results of the examination of the urine for the precipitable pneumococcus substance in 88 cases of pneumonia due to the fixed types of pneumococcus I, II and III. Of these 88 cases, 35 were Type I, 28 were Type II, 8 were Type II (atypical), and 17 were Type III. Repeated tests of the urine were made during the course of the disease from within twelve hours after onset in one instance to the fifty-eighth day in another. Of the 35 cases due to Type I infection, 20 were positive and 15 negative. A positive blood culture occurred in 13 of the 35 cases.

Among the 13 cases with positive blood culture, 9 showed a positive urine reaction and 4 gave a negative result. Of the 20 cases

TABLE IV

Pneumococcus Precipitin Reaction in the Urine during Lobar Pneumonia

Case No.	Urine reaction.	Day of disease when urine was first tested.	Day of disease when urine was first positive.	Duration of positive reaction.	Blood culture.	Serum treatment.	Result of disease.	Remarks.
					Pneumococcus Type I infection			
				days				
2816	++	6	6	6	+	+	Died	
2936	+	6	6	18	−	+	Recovered	
2968	++	5	5	14	+	+	"	
2858	+	3	4	1	−	+	"	
2996	+	3	3	15	−	+	"	
2891	+	3	3	5	−	+	"	
2965	+	6	6	16	−	−	"	
2952	+	2	5	3	−	+	"	
2804	+	6	6	26	−	+	"	
2955	++	6	6	26	+	+	"	
2925	+	1	1	1	+	+	"	
2908	+	5	13	5	−	+	"	
2924	+	5	5	22	−	+	"	
2913	+	5	5	1	−	+	"	
2945	+	5	5	29	+	+	"	
2906	+	2	2	31	+	+	"	Delayed resolution.
2852	+	4	4	2	+	+	"	
2949	+	8	11	24	−	+	"	
2901	+	5	5	4	+	+	Died	
2917	−	6	−	−	−	+	Recovered	
2814	−	2	−	−	−	+	"	
2944	−	5	−	−	−	+	"	
2874	−	3	−	−	+	+	"	
2815	−	4	−	−	−	+	"	
2824	−	3	−	−	−	+	"	
2821	−	6	−	−	−	+	"	
2984	−	7	−	−	−	+	"	
3020	−	3	−	−	+	+	"	
3043	−	3	−	−	−	+	"	
3011	−	5	−	−	+	+	"	
2883	−	4	−	−	−	+	"	
2954	−	4	−	−	−	+	"	
2880	−	3	−	−	+	+	"	
3019	+	4	8	42	+	+	" (empyema)	
3033	−	2	−	−	−	+	Recovered	

TABLE IV—*Continued*

Case No.	Urine reaction.	Day of disease when urine was first tested.	Day of disease when urine was first positive.	Duration of positive reaction.	Blood culture.	Serum treatment.	Result of disease.	Remarks.
Pneumococcus Type II infection								
				days				
2869	++	2	2	2	+	+	Died	
2922	+	3	3	40	+	+	Recovered	
3006	+	2	2	8	−	−	Died	
2885	+	2	2	2	−	+	Recovered	
2845	++	5	5	2	+	+	Died	
2868	+	4	7	3	−	−	Recovered	
2899	−	1	−	−	−	−	"	
2879	−	2	7	1	+	+	"	
2892	++	5	5	2	+	−	Died	
2834	++	5	5	5	+	+	"	
2991	+	1	2	58	−	−	Recovered	
2854	−	3	5	1	−	−	"	
3003	+	7	7	13	−	−	"	
2827	++	3	3	1	+	−	Died	
2746	+	3	6	9	+	−	"	
2881	+	6	6	2	−	−	Recovered	
2786	−	6	−	−	−	−	"	
2896	−	7	−	−	−	−	"	
2926	−	4	−	−	−	−	"	
2897	+	3	4	1	−	+	"	
2886	+	3	3	6	−	−	"	
2890	+	3	3	4	+	+	Died	
2971	+	7	14	10	−	−	Recovered	
2825	++	1	1	5	+	−	Died	
3031	+	3	3	5	+	+	"	
3047	+	3	3	?	−	−	Recovered	
2937	−	1	−	−	−	−	"	
2934	−	4	−	−	−	−	"	
Pneumococcus Type II (atypical) infection								
2861a	−	3	−	−	+	−	Recovered	
2878b	−	4	−	−	−	−	"	
2822b	−	5	−	−	−	−	"	
2831x	+	4	4	3	−	+	"	
2864b	+	8	8	2	+	−	Died	
2960x	−	1	−	−	−	−	"	
2963b	+	4	7	13	−	−	Recovered	
2935b	−	1	−	−	−	−	"	

with positive urine reaction, 2 died; of the 14 negative cases all recovered. All these instances of Type I infection were serum treated.

TABLE IV—*Concluded*

Case No.	Urine reaction.	Day of disease when urine was first tested.	Day of disease when urine was first positive.	Duration of positive reaction.	Blood culture.	Serum treatment.	Result of disease.	Remarks.
Pnemococcus Type III infection								
				days				
2838	−	3	−	−	−	−	Recovered	
2889	−	7	−	−	−	−	"	
2797	++	2	2	5	−	−	Died	
2898	++	5	5	3	+	−	"	
2947	++	5	5	30	−	−	Recovered (empyema)	
2812	+	2	5	1	+	−	Died	
2783	+	7	7	1	+	−	"	
2919	+	5	6	4	−	−	"	
2800	+	3	3	3	+	−	"	
2849	+	3	3	2	+	−	"	
2927	+	2	6	4	−	−	Recovered	
2973	+	3	10	4	−	−	"	
2911	+	2	2	13	−	−	"	
2837	−	1	−	−	−	−	"	
2972	+	1	6	2	−	−	"	
2485	−	6	−	−	+	−	Died	
2918	−	2	−	−	−	−	Recovered	

Summary of Urine Reaction

Type.	Total number of cases.			Per cent. positive.	Positive blood culture.	Positive urine reaction.		Negative urine reaction.		Fatal cases showing urine reaction.	
	Examined.	Positive.	Negative.			With blood culture positive.	With blood culture negative.	With blood culture positive.	With blood culture negative.	Positive.	Negative.
I	35	20	15	57.1	13	9	11	4	11	2	0
II	28	20	8	71.4	11	10	10	1	7	10	0
II (atypical) .	8	3	5	37.5	2	1	2	1	4	1	1
III	17	12	5	70.5	6	5	7	1	4	7	1
	88	55	33	62.5	32	25	30	7	26	20	2
IV	10	0	10	0	2	0	0	2	8	0	2
Cases of respiratory disease due to organisms not pneumococcus .	14	0	14	0	2	0	0	2	12	0	2

The administration of serum in Type I pneumonia often results in the temporary disappearance of the substance from the urine. Upon cessation of treatment the soluble substance may reappear in the urine.

Of 28 cases of Type II infection, 20 gave positive precipitin reaction in the urine, and 8 were negative. A positive blood culture occurred in 11 of the 28 cases. Among the 11 cases with positive blood culture, 10 gave a positive urine reaction and 1 a negative result. Of the 20 cases with a positive urine test, 10 died; of 8 negative cases all recovered.

Among 8 cases of infection with atypical Type II pneumococcus, 3 gave a positive precipitin reaction in the urine and 5 a negative reaction. Inasmuch as a normal Antipneumococcus Serum Type II was used in determining the presence of soluble substance in the urine of individuals infected with atypical Type II pneumococcus, a lower percentage of positive urine reactions should be expected in this series, since the precipitin titer of normal Type II serum is low for these atypical organisms.

Seventeen cases of pneumonia due to infection with Pneumococcus Type III were studied. Pneumococcus precipitinogen was demonstrated in the urine of 12 of these instances, and was absent in 5. A positive blood culture was obtained in 6 of the 17 cases. Of the 6 cases having pneumococcus septicemia, 5 showed a positive precipitin reaction in the urine. Seven of the 12 cases giving a positive urine test died, while 4 of the 5 negative cases recovered.

A summary of 88 cases of pneumonia due to the fixed types of pneumococcus shows that the soluble substance of pneumococcus origin was demonstrable in the urine of 55 (62.5 per cent.) of these patients at some stage of the disease and in 39 instances was positive on the first examination. Among the 55 cases with a positive precipitin reaction in the urine, 20 had a fatal outcome, giving a mortality of 36.4 per cent., and of the 33 cases with a negative urine test, 2 died; a mortality of 6 per cent. In addition to the 88 individuals suffering from pneumonia due to the fixed Types I, II and III, 10 cases of Type IV pneumonia and 14 cases of respiratory disease due to other organisms were studied for the presence of a precipitin reaction in the urine. Each urine was tested

with standard Antipneumococcus Sera Types I, II and III. In no instance was a positive reaction obtained at any stage of the disease, a fact which establishes beyond doubt the specificity of the reaction.

In addition to the presence of the soluble substance of pneumococcus origin in the blood and urine, it has also been found in other body fluids. In certain cases it can be readily demonstrated in pleural fluids and pericardial exudates and in the spinal fluid of pneumococcus meningitis.

Certain facts have been ascertained concerning the chemical characteristics of this substance. The specific substance is not destroyed by boiling. It is readily soluble in water and is precipitable in acetone, alcohol, and ether, after which it may be easily redissolved in water. It is precipitated by colloidal iron, and does not dialyze through parchment. The immunological reactions of the substance are not affected by proteolytic digestion with trypsin and it is not split by urease. The determination of total nitrogen and nitrogen partition on the active substance obtained by repeated precipitation with acetone and alcohol shows the substance to be of protein nature or to be associated with protein.

One of the chief points of interest in the discovery of the soluble substance of pneumococcus is whether this substance is in any way responsible for the intoxication which attends pneumococcus infection. Studies to ascertain the answer to this question are being actively carried on at the present time but have not as yet progressed to the point at which a definite answer can be given. It may be said, however, that its toxicity is in no way comparable to that of diphtheria toxin. On the other hand, it possesses a degree of toxicity which, exhibited throughout the course of an infection, may account for the signs of intoxication in lobar pneumonia.

Discussion. The preceding experimental data have shown that a specifically reacting substance of pneumococcus origin occurs in the bacteria-free filtrates of young cultures of pneumococcus and also in the blood serum and urine of patients during lobar pneumonia. The occurrence of specifically precipitable substances in the cell-free filtrate of bacterial cultures has been known ever since the early observation of Kraus. It has been abundantly confirmed

by other investigators with a variety of bacteria. In general, the presence of this precipitable substance has been demonstrated in culture fluids so old that an opportunity has occurred for cell death and disintegration and consequent solution of bacterial protein. In this paper it is shown that there is present in solution in the culture fluid in which pneumococcus is grown, a soluble substance in considerable amounts at a time when no cell death or disintegration has occurred. Consequently this substance does not represent dead dissolved bacterial protein, but the elaboration and passage into solution of a substance which is the product of the life activity of the cell. In addition to the evidence already cited in support of this fact, it has been demonstrated that the soluble substance is present in culture fluids in considerable concentration at a time when no hemolysin is present. This pneumococcus hemolysin is an intracellular body which does not appear in culture fluids until destruction of the bacterial cell has taken place; hence if the soluble substance described were purely of intracellular origin the curve of its concentration in culture fluids would be coincident with that of the hemolysin. This, however, is not the case, for the curve of hemolysin does not begin to rise until a time when the curve of the soluble substance has almost attained its maximum elevation.

The formation of a soluble substance by the pneumococcus on growth *in vitro* suggested the probability that an analogous substance would be formed on growth of the organism in the animal body and because of the readiness with which the substance passes into solution one would expect no difficulty in demonstrating it in the body fluids of experimentally infected animals. Examination of the blood and urine of rabbits infected with pneumococcus has shown this substance to be present in considerable quantities following intraperitoneal infection. Ascoli and Valenti[1] have demonstrated in the organs of animals infected with anthrax a substance specifically precipitable with antianthrax serum. Bail[2] has shown the presence of a substance in the exudates of animals

[1] Centralbl. Bakteriol., 1te Abt., Ref., 1911, xlviii, 243.
[2] Arch. Hyg., 1905, lii, 272; 1905, liii, 302.

infected with anthrax which, when the fluids were freed from bacteria, increased the infectious power of anthrax bacilli. This substance he has called aggressin, and he considers it to be an excretory product of the anthrax bacillus which favors the invasion of animal tissues by this organism. It is possible that the substances described by Ascoli and Valenti and Bail are similar in the mechanism of their formation to the soluble substance produced by the pneumococcus. Although our study of other bacteria has been rather limited, it has been demonstrated that certain other species, such as meningococcus, *Bacillus typhosus*, and *Bacillus dysenteriæ*, also give rise to soluble material during their growth in fluid media.

A study of the serum of patients suffering from lobar pneumonia has shown that this soluble specific substance is also present in the circulating blood during the course of the disease in man. It gives a specific precipitin reaction with antipneumococcus serum corresponding in type to the organism with which the individual is infected. This soluble precipitable substance in human serum is less frequently present in demonstrable quantities than in the serum of experimentally infected animals. However, it has been found both when pneumococci are present in the circulating blood and when by blood culture organisms are absent. Complement-fixation, as well as the precipitin reaction, may be used for the demonstration of this substance in serum. Although the soluble substance is relatively infrequently present in demonstrable quantities in the circulating blood, it is not unlikely, from the fact that the substance appears in a much larger percentage of cases in the urine, that it is much more commonly present in the blood than observed, but in quantities that are below the threshold of demonstration.

A study of the urine in 112 cases of lobar pneumonia and closely related respiratory diseases has shown that in 62.5 per cent. of pneumonia due to Pneumococcus Types I, II and III, a substance is excreted in the urine which reacts specifically with antipneumococcus serum of the type corresponding to the organism with which the individual is infected. This substance may appear as early as twelve hours after the initial chill, or may appear for the

first time at a later stage of the disease, and may continue to be excreted for many days after recovery has occurred. In certain instances in which excretion occurred over a long time, its persistence in the urine could be explained by delayed resolution, a condition which represents the passage of the acute pneumococcus infection of the lung into one of a more chronic character. In other instances of continued excretion not explainable on these grounds, the substance must have been stored in the tissues and must have passed into the circulating blood to be excreted by the kidneys without loss of its specific character. It is the rule to find the substance in the urine when pneumococcic septicemia exists. The amount of precipitable substance in the urine seems to be a measure of the severity of the infection. This fact may be dependent upon the quantity of the substance being directly proportional to the actual amount of infection or it may be that the amount of this substance formed bears some relationship to the virulence of the particular strain of pneumococcus responsible for the infection. Most of the instances which fail to show the presence of a precipitable substance in the urine recover, whereas the mortality is high among those in which its presence is demonstrable. If large amounts are excreted the outcome is usually fatal, unless this result is prevented by the administration of antipneumococcus serum. The specific precipitin test in the urine is therefore of considerable prognostic value. It may also be used in making a rapid diagnosis of the type of organism with which an individual is infected and in our experience a positive test in the urine is quite as reliable as the agglutination of the organism isolated from the sputum. The precipitin test in the urine, however, should not supplant the usual diagnostic technic in the determination of the type of pneumococcus.

Eleven years ago Fornet[1] claimed to have demonstrated in the serum and urine of patients suffering from typhoid fever a substance specifically precipitated by antityphoid serum. From what we now know it would seem likely that his observations were correct despite the fact that subsequent investigators failed to confirm them.

[1] München. med. Wchnschr., 1906, xxxviii, 1862.

Ascoli[1] has shown that precipitinogen may pass the kidneys and appear in the urine where it exhibits its specific reaction. We have been able to show that if rabbits are inoculated intravenously with soluble pneumococcus material a specific precipitin reaction can be obtained in the urine within twenty-four hours and that the specific substance continues to be excreted for a number of days. In such an experiment the material injected contained no formed living pneumococci. Pettit[2] has demonstrated that if rats are injected with diphtheria toxin, this substance can be shown to be excreted in the urine in active form following the inoculation.

SUMMARY. 1. A specifically reacting substance of bacterial origin is present in the cell-free fluids of young cultures of pneumococcus. This substance is present when the organisms are growing at their maximum rate and undergoing little or no cell death, and consequently its presence is not dependent upon cell disintegration but represents the extrusion of bacterial substance by the living organism.

2. The blood and urine of rabbits experimentally infected with pneumococcus contain a similar specific soluble substance during the early hours of the infectious process.

3. Human beings suffering from lobar pneumonia have in their blood and more frequently in their urine a specific soluble substance of pneumococcic origin. The amount of this substance present in the urine varies in different individuals and the presence of a large amount is of unfavorable prognostic import. This specific precipitin reaction in the urine is of diagnostic value.

4. Rabbits injected with soluble pneumococcus material continue to excrete this substance for a considerable period of time.

5. The specifically soluble substance obtained from bacterial cultures and from the urine during infection is not destroyed by boiling, by precipitation with alcohol, acetone, or ether, or by trypsin digestion.

6. Studies are in progress at this time on the degree of toxicity and on the antigenic properties of the substance.

[1] Cited in Kolle, W., and von Wassermann, A.: Handbuch der pathogenen Microorganismen, Jena, 2nd edition, 1913, ii, 750.

[2] Ann. Inst. Pasteur., 1914, xxviii, 663.

DISCUSSION

Dr. Cole: Dr. Dochez in his presentation today has not emphasized the importance of their observations in facilitating the early determination of the type of pneumococcus, causing the infection in the individual case. Unfortunately, from a diagnostic stand-point, the precipitin reaction in the urine appears only in the very severe cases, and only fairly late in the disease. In about a third of the cases, however, the detection of the specific substance in the urine has been of great importance in diagnosing the type of infection present.

THE CAUSATION AND CURABILITY OF CERTAIN LONG-STANDING ALBUMINURIAS

By DAVID RIESMAN, M.D.
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During the past few years a number of cases of albuminuria have come to my notice in which investigation showed the existence of a local focus, the removal of which led to the disappearance of the albuminuria. Thanks to the work of Billings and his school, we know the importance of foci of infection in the production of systemic disease. It is of interest to note that as early as 1802 Benjamin Rush pointed out in a letter the relation between systemic disease and caries and abscess of the teeth.

That severe local infections, such as ulcerative endocarditis, tonsillitis, and indeed most other acute infections are capable of producing nephritis of the parenchymatous type is of course a long-established fact. With this form of nephritis, which is an immediate result of the acute toxemia, I am not dealing. The type to which I desire to call attention is entirely devoid of acute features and has all the earmarks of chronic renal disease. We know how futile is the attempt in the majority of such cases to remove the albumin from the urine by means of drugs or by diet.

These insidious albuminurias are often found in apparently healthy men who in full confidence apply for life insurance, only to be refused temporarily or permanently, because of the trace of albumin in the urine. Among adolescent subjects some cases have been classed as cyclic, orthostatic or postural albuminuria, a contribution that has as yet no very satisfactory explanation. These cases are rather easily recognized; they give, as Barker has shown, normal phenolsulphonephthalein outputs; and in other ways behave as

cases of a non-progressive type of renal irritation. Apparently the worst that can be said of them is that they bar the patient from life insurance.

While many cases of albuminuria of slight degree and springing from no obvious cause are due to early interstitial nephritis, there are some in which a careful search reveals a disease focus that stands in etiological relation to the albuminuria. Let me illustrate this by a few examples:

Case I.—J. J. H., a boy, aged nine years, came under my care because of poor and capricious appetite and general lack of vitality. He had been a difficult "feeding case" as an infant, but had not had any special diseases. From birth he was sensitive to protein, particularly egg protein, which caused hives, as his mother said, "almost before he swallowed it." Once he passed a little gravel. The tonsils and cervical glands were enlarged, but the boy was not a mouth-breather. There was also some enlargement of the spleen. The urine was very scanty and for a year or more had contained a small amount of albumin and occasionally hyaline and granular casts. There was no edema. All manner of treatment was tried without producing any marked changes in the urine either in quantity or in quality.

Although the boy had never had a genuine attack of tonsillitis, I thought it best to have the tonsils removed since they looked unhealthy. They were extirpated under ether on April 1, 1913, nearly two years after the discovery of the albuminuria. Both tonsils were found to contain cheesy masses and one an abscess. There was also a large adenoid. The second specimen of urine examined after the operation was free from albumin. Then for a little while traces reappeared, but at the end of about six months both albumin and casts had entirely vanished. The appetite at present leaves nothing to be desired, and the lad is one of the finest and most agile of his age.

Case II.—A man, aged forty-two years, a veterinary surgeon, came under my observation in 1913, stating that for years he had had pain in the right lower abdomen which had sometimes been looked upon as appendicitis, sometimes as renal colic. He had never passed blood or gravel, and only once, for about a week in 1911, he had passed pus. He had become more or less reconciled to the diagnosis, made by many medical examiners, of Bright's disease. The urine showed, when I examined it, just as it had done for many years, a small amount of albumin. On January 20, 1913, having had the confirmative evidence of an *x*-ray examination, a successful operation for the removal of a stone was performed by Dr. B. A. Thomas. The albumin disappeared quite promptly. When I last saw the patient he seemed to be entirely well.

Case III.—The next patient was a young man, aged twenty-one years, a college student, who was sent to me by Dr. W. P. Walker, of South Bethlehem, because of albuminuria which had been discovered during an examination for life insurance. Since 1909 the boy had had four sharp attacks of tonsillitis, this notwithstanding the fact that he had had an operation for adenoids and enlarged tonsils in 1907. Measles, chicken-pox and whooping-cough he had passed through in early life. The urine had a specific gravity of from 1016 to 1024, and contained albumin and sparse hyaline casts, and occasional red blood cells. His blood-pressure was 120 systolic and 80 diastolic; weight 109½ pounds. The phenolsulphonephthalein test showed 53 per cent. in the first two hours and 15 per cent. in the third hour. The onset of elimination was somewhat delayed, requiring twenty minutes. The quantity of urine was about normal.

While at Yale he was seen by Dr. Tileston, and on one occasion by Dr. Pratt, of Boston. Both found the same condition that I have described.

In June, 1914, the young man, with a number of other students fell ill with sore throat, after eating at a certain restaurant. Feeling better at the end of twenty-four hours he went to his home in Bethlehem, where he immediately had a relapse. The throat was intensely inflamed, and on the swollen tonsils there were discovered follicular spots as well as areas of whitish exudate. The patient was extremely weak and prostrated, and had great difficulty in swallowing. I saw him with Dr. Butler, and felt sure that he had streptococcic sore throat. After his recovery, which ensued without serious interruption, the tonsils from which he had suffered so much during the preceding four or five years were thoroughly extirpated. The albumin disappeared from the urine thereafter, and the last account I had from the young man was that he was perfectly well.

When on one occasion I discussed the subject of albuminuria due to focal conditions with Dr. B. A. Thomas, he told me that he could supply me with the histories of several striking cases. He has been kind enough to do so, and I copy one:

The patient, a young man, aged twenty-two years, consulted Dr. J. C. Birdsall, Dr. Thomas's assistant, in February 15, 1915, because of albuminuria discovered on January 1, 1914, during examination for life insurance. The urine showed a light cloud of albumin but no tube casts. Examination of the pharynx revealed diseased tonsils. A tonsillectomy was advised, which was done during the summer of 1915. On October 9 the albumin still showed a cloud of albumin. On December 17 the patient was seized with an attack of bronchitis; sputum culture revealed the pneumococcus and the Staphylococcus albus. An autogenous bacterin was pre-

pared, of which the patient received a number of injections. The urine was examined several times during the next two months, and on every occasion was found free of albumin.

Dr. Thomas also tells me that he has seen a number of instances of chronic albuminuria in syphilitic patients in whom the albuminuria entirely disappeared after antiluetic treatment.

The point that I desire to bring out in this brief paper is that cases of long-standing but otherwise mild albuminuria should not be looked upon as incurable unless evidence on the part of the cardiovascular system or testimony given by functional tests clearly demonstrates that the kidneys are diseased. This also applies to the so-called orthostatic or postural albuminurias of adolescents. The albuminuria may be kept up by disease of the tonsils (which is not always discoverable by simple inspection), by dental abscesses, by other infective foci, or by the presence of a stone. It may be made to disappear entirely, at least in some cases, by the removal of the offending focus. This gratifying result does not always set in immediately, but sometimes only after a number of months. The physician should therefore not be too soon discouraged. It is probable that kidneys which have been for a long time the seat of slight irritation will always be somewhat sensitive, whence it follows that patients cured of albuminuria should remain under medical observation for a number of years.

DISCUSSION

Dr. Janeway said the subject presented by Dr. Riesman is one of most practical interest and importance to all of us who must see cases that are taken on the strength of the urine examination, as having a dangerous albuminuria. Going back historically to the early days of the first recognition of albumin in the urine as the essential evidence of Bright's disease they often condemned patients to the diagnosis and the corresponding prognosis of chronic Bright's disease. He had of late been greatly interested in looking through the historical development of our knowledge of albuminuria, realizing that it was not until the 70's, roughly forty years after Bright's original publications, and some seventy or eighty years after the

original recognition of the essential diagnostic significance of albuminuria, that people woke up to the fact that there were cases of albuminuria which did not signify a chronic, progressive disease of the kidney, and the first recognition of that came from the publication of Moxon, which immediately brought out a group of similar isolated cases observed by his various colleagues in London, including Wilkes, who spoke about the matter in young people; and from that through Pavy's work, and finally Stirling's came the recognition of postural albuminuria as probably the most important single cause of error in the diagnosis of chronic nephritis. Stirling laid the foundation of our present knowledge of the subject and really gave, what seemed to the speaker, the proper name to the condition, namely: postural albuminuria rather than the name orthotic or orthostatic albuminuria, which was given it somewhat later by Heubner, because, while Heubner's name indicates the necessity for the upright posture, Stirling's name does not restrict the condition, and the work of Jehle has shown that you can produce this same type of albuminuria by lordosis with the patient in the horizontal position. This makes the designation orthostatic albuminuria incorrect for embracing all the cases.

Dr. Janeway said children or young people with postural albuminuria were coming to their dispensary and hospital with considerable frequency and often were the cause of very grave difficulty in diagnosis. From time to time one sees a patient whose albuminuria has been discovered after an attack of acute tonsillar infection, and a diagnosis of acute nephritis has been made frequently and the patient has then been rested over a long period. In these cases it may be extremely difficult to be certain whether the postural albuminuria is the only condition which exists, or whether that is the combination of the postural element—whatever its authentic explanation may be—with an acute or subacute inflammatory processes in the kidney. Politzer, of course, has, in his book, *Ren Juvenum*, emphasized that view, and has antagonized the view of Jehle that the condition is altogether a mechanical affair. Politzer holds that these children are constitutionally predisposed, because of their type and build, to albuminuria, from causes which in a normal child would not bring it out; and the essential cause, he believes, is inflammation of the tonsillar ring.

There are cases which lend color to Politzer's view, but, for the most part, as the speaker and his associates have been seeing those cases in Baltimore, they conform to Jehle's type, with upper lumbar lordosis, with the occurrence of large amounts of albumin in the urine on standing, a large amount of protein precipitable by acetic acid in the cold; also with occurrence of an oliguria and a diminished salt output during periods of the erect posture, particularly if lordosed.

There are certain practical points to be brought out in connection with the recognition of these cases. One is that it is a mistake to suppose that if

you lordose the patient for a half or three-quarters of an hour and then put him back to bed that the minute he goes back to bed the albuminuria will cease. The kidney does not recover with that rapidity. There must be a second observation secured in bed before one can be reasonably sure. Another matter is the testing out of the difference between the effect of simple posture, or as Jeanneret, in a very interesting recent paper, has brought out, a rigidly maintained posture in the erect position, which is the most certain way of bringing out this albuminuria, and the effect of exercise.

It has been known, ever since Stirling's day, that if these patients run around in the erect posture they do not have albuminuria; if they stand in the erect posture, they get very marked albuminuria. Nephritic albuminuria is usually increased markedly by exercise. The speaker has had patients with postural albuminuria exercise on machines in the gymnasium, or in ways which will avoid a rigid or erect posture, and frequently has put them through an hour's hard exercise without any albuminuria whatever; whereas an hour erect, in a rigid position, would bring out extreme albuminuria. He has been employing that test, and while not satisfied that it is a clean-cut method of discrimination, he has seen cases in which it appealed to him as of real value; and one of his assistants, Dr. Smith, is making a study of those cases, in order to determine whether cases of a nephritic albuminuria will respond that way.

Calculus may be a suspected cause of albuminuria, as in a patient who had always albumin and hyaline casts in his urine, without any suggestion that he had a stone. He was radiographed, with the disclosure of stone; and with the operation for the removal of the stone the albuminuria and the hyaline casts completely disappeared. The other type of albuminuria that the speaker would call attention to in adults is the albuminuria occurring after hard exercise, which Leube first described in his study of soldiers. There was an important case which the speaker's father saw in the earlier days of his practice, that of a man who was refused life insurance because of the constant appearance on the life insurance examination of quantities of hyaline casts in his urine. The speaker's father, having certain detective instincts, made up his mind he would hunt the thing down. He found that the man went for his life insurance examination always in the late afternoon; that always in the afternoon it was his custom to have a cold shower-bath following a bout at the gloves; and that he went to the life insurance examination immediately succeeding the boxing and the cold shower. The speaker saw this man thirty years after his father had made this discovery, and he was then still free from renal disease, though he had been constantly refused life insurance. That is where we have a quarrel sometimes with the life insurance examiners, though their point of view has to be different, necessarily, from ours.

Dr. Meltzer said he would like to supplement the title of Dr. Riesman with a still more striking title given by Osler. It is not only curability. You will all remember, probably, Dr. Osler's article with the title, "The Advantage of Albuminuria."

Dr. Thayer merely wished to add his testimony to that of Dr. Riesman as to the relative frequency with which one meets just such cases as described in the paper. One case especially was recalled, as occurring in the last ten years, of a rather overgrown boy, aged fifteen years, brought to the speaker's office in order that he might give suggestions as to how a warm climate might act to doctor up his chronic nephritis. The family had thought of going to Cuba. On examination most obvious adenoid and tonsillar affections were discovered, and it was learned that the boy had seen a homeopathic surgeon, and the year before had had both adenoids and tonsils removed. It had been a homeopathic operation in every sense of the word; and following complete tonsillectomy and removal of the adenoids the albuminuria disappeared entirely and the patient did not have to go to a warm climate for the winter.

With regard to Dr. Janeway's contribution, it was his impression that a very considerable proportion of normal individuals showed albuminuria immediately following a sharp, cold bath.

Dr. Rowntree said in the last few months he had seen 4 or 5 cases of albuminuria wherein it was impossible for him to decide whether the patient had nephritis or not. All of these cases showed perfectly normal renal function, but albuminuria was persistently present. In one case there was constantly present a mild grade of albuminuria, glaucoma, and beginning eye-ground changes which were thought to be of renal origin. Going over this man he found he had a perfectly normal renal function, showing no other signs of nephritis beyond this albuminuria, with occasionally a few casts. These changes might have been arteriosclerotic in origin, though the peripheral vessels were fairly soft and the blood-pressure normal. The man had very bad tonsils. Dr. Rowntree sent him back, with the report that probably the tonsillar condition was the basis for the albuminuria and secondarily of decreasing vision. The tonsils were removed about six weeks ago, with some improvement in vision.

Marked changes in albuminuria can be wrought at times as the result of removal of diseased tonsils or of draining of sinuses. He had been disappointed on the whole in the results of the removal of foci of infection in nephritis. In attempting to recall cases in which he had seen definite, permanent improvement only three or four instances came to mind in which the removal of the foci of infection definitely removed the albuminuria.

Dr. Fussell said we all have seen many cases in which we are not able to fix definitely the focus of infection if there is a focus. Another great difficulty had been, after finding the focus of infection, for instance the teeth, by careful *x*-raying, to get the dentists to decide just what amount of treatment should be given. Just before leaving Philadelphia the speaker had had under his observation 2 cases of very bad teeth from the *x*-ray stand-point. One of them was in the hands of a dentist who declared he would draw every tooth in that individual's mouth, at least all but two, the only ones not apparently diseased. In the other case the dentist said, "This is all nonsense," that he could cure this man without drawing any of the teeth. The great question in Dr. Fussell's mind with many of these cases is, What shall we do particularly when the teeth seem to be the focus of infection? Shall we have the teeth drawn; shall we have a consultation with any dentist; what shall we do?

Dr. Thayer further said that Dr. Fussell rightly estimated dentistry as a very important specialty of surgery. The dentist should be a surgeon and a specialist in surgery. He should be present at our meetings; we should have our symposium with him; and the sooner we of the medical profession bring it about that the dentist is made a regular surgeon, that he has to take the same course that we do, and that his specialty is just as much surgery as abdominal surgery or gynecology, the better it will be for the medical profession.

OBSERVATIONS UPON CALCIUM IN RICKETS AND TETANY

By JOHN HOWLAND, M.D.

AND

W. McK. MARRIOTT, M.D.

BALTIMORE

(From The Harriet Lane Home, Johns Hopkins Hospital and the Department of Pediatrics of the Johns Hopkins University)

The objects of this study were to investigate the calcium content of the blood in rickets, to determine if possible if the low calcium content of the bones which obtains in rickets could be referred to any alteration in the amount of calcium in the blood, also to investigate the calcium content of the blood in that closely related disease, tetany, which is the most frequent cause of convulsions in infancy and of the hyperexcitability of the nervous and muscular system; finally to obtain, if possible, clear evidence of the benefit of therapeutic procedures in tetany.

Last year Marriott and I reported results upon the determination of Ca in the serum of patients with rickets and tetany. In the past year we have extended our observations. I should like at the present time to speak only of the calcium, reserving consideration of the magnesium until some future time.

Method. It was necessary to develop a method that would allow duplicate determinations to be made with a small amount of blood and with sufficient accuracy. This we have done. The method is sufficiently exact to determine the calcium in 2 c.c. of serum with an error of not more than 5 per cent. The method is time-consuming and requires a considerable degree of experience in the various manipulations and in the final readings, but others

beside ourselves have used it with as much success as have we. The method depends upon the ability of oxalates in an acid solution to decolorize a solution of ferric thyocyanate. The calcium of the serum is isolated as the oxalate; this is then dissolved in dilute hydrochloric acid and is determined by comparison with the decolorization produced by a known amount of oxalic acid. We have used blood serum in our determinations, for there is practically no calcium contained in the corpuscles. This obviates the necessity of removing the iron. The results upon serum under normal conditions are almost exactly twice as great as in whole blood, 50 per cent. of which by volume is composed of corpuscles.

We determined first the calcium in the serum of normal persons. The amounts found are given in Table I as calcium in 100 c.c. of serum.

TABLE I.—NORMAL. MILLIGRAMS OF CALCIUM PER 100 C.C. OF SERUM

Placental serum	11.3
Placental serum	11.0
Placental serum	10.8
Placental serum	10.7
6 weeks	11.0
3 months	10.0
3 months	11.0
5 months	10.8
15 months	11.0
Adult	11.2
Adult	11.3
Adult	9.2
Adult	10.0
Adult	10.3
Adult	11.0
Adult	9.8

It will be seen from the table that the quantity of calcium in placental serum and in the serum of normal patients, no matter of what age, is singularly constant. In almost all instances, no matter what the age, and in all instances with infants it was above 10 mgm., and it is seldom more than 11 mgm.

As rickets so frequently is found associated with tetany it was necessary to determine what changes, if any, in the calcium of the serum result from rickets. We have therefore studied a considerable number of cases of rickets. It is well recognized from pathological

studies, particularly those of Schmorl, that rickets is often at least not a continuous process. There occur periods of remission and exacerbation, sometimes several in succession. These are difficult to determine from clinical symptoms alone, especially if one relies upon alterations in the bones. In these periods of remission it has been shown by metabolism studies that calcium is retained; in the periods of exacerbation there is either an insufficient retention or an actual negative balance of calcium. In order to obtain if possible blood from patients with rickets in progress we have made our studies only in the winter and spring months, when it is known that rickets is most prevalent and apt to be active. We have also studied quite a series of infants with early manifestations of the disease.

We have divided our cases into the "mild" and "severe," meaning by mild those that showed few changes in the bones and that did not have an enlarged spleen or craniotabes. Severe we have called those with sweating around the head, with craniotabes, enlarged spleen, and with severe and apparently increasing changes in the bones. We realize that this is a purely arbitrary division, but it seems the best that can be done.

TABLE II.—RICKETS. MILLIGRAMS OF CALCIUM PER 100 C.C. OF SERUM

No.	Age.	Type of rickets.	Calcium.
1	4 months	Active	10.9
2	4 months	Active	9.0
3	4 months	Active	10.5
4	4 months	Active	7.9
5	4 months	Active	9.0
6	4 months	Active	8.0
7	4 months	Active	9.0
8	4 months	Active	8.3
9	4 months	Active	9.3
10	6 months	Mild	10.9
11	6 months	Mild	10.7
12	6½ months	Moderate	8.6 9.0
13	8 months	Mild	10.9
14	8 months	Moderate	9.0
15	8 months	Marked	10.5
16	9 months	Marked	9.0
17	10 months	Mild	8.0
18	12 months	Mild	9.8
19	14 months	Mild	8.8
20	20 months	Marked	10.0
21	23 months	Very severe	9.3

In both of these classes of rickets the tendency is for the calcium to be low. While cases are found in both classes with a normal calcium content, in general it is in the neighborhood of 9 mgm., and in three or four it was between 7.5 and 8.5.

It has been assumed from indirect evidence by most of the best students of rickets that the Ca of the blood is not low but that the Ca is not deposited in the bones and cartilages on account of some disturbance in the bones and cartilages themselves. It would seem that this assumption is only partially correct. The Ca of the blood is often lower than normal, and yet it does not seem to us likely that this moderate reduction of the calcium determines rickets. There is probably some other factor involved.

Tetany. The relation of rickets and tetany is a close one. Tetany is usually found in rachitic patients. It seemed advisable to investigate the relationship between these diseases so far as the calcium in the blood is concerned. MacCallum and Voegtlein and MacCallum and Vogel have shown that in the parathyroid tetany of dogs the Ca of the blood is low in amount. There have been no satisfactory determinations of Ca in human tetany.

Tetany varies greatly in severity. It may be latent and only to be recognized by hyperexcitability to the galvanic current or it may be active with stormy symptoms.

We have studied a number of active cases. All had convulsions, many had carpopedal spasm and spasm of the glottis and other characteristic symptoms of tetany, such as Trousseau's sign and the facial phenomenon of Chvostek. All demonstrated a marked galvanic hyperexcitability, as shown by a cathodal opening contraction with a current less than 5 ma. In all of these there was a distinct lowering of the Ca in the blood (Table III). It will be seen that when the convulsions occur the Ca in the serum is usually as low as 6 mgm. per 100 c.c., that is about half the normal amount. We have studied cases of convulsions not due to tetany and have found no diminution in the amount of Ca. It seems therefore that the Ca determination may be a matter of great diagnostic importance.

Marriott and I showed last year that when the inorganic phosphate of the serum is very much increased, as it is in some cases

of severe nephritis, the calcium is greatly diminished. In infantile tetany the calcium reduction does not depend upon an accumulation of phosphate in the serum, as we have found the phosphate within normal limits.

As tetany usually exists on a rachitic basis, that is, practically all cases of tetany show evidences of rickets clinically or post-mortem, it is possible, indeed likely, that the cases of rickets that we have studied with exceptionally low Ca may have been in reality cases of latent tetany. It is impossible to speak definitely in regard to this, as we have not yet studied cases of latent tetany.

Treatment. Since active tetany is invariably accompanied by a low calcium content of the blood it would seem the rational procedure to give Ca. This is not an original idea, but there is no uniformity of opinion regarding the value of Ca.

We have used it in 5 cases. In all it brought about immediate improvement in the symptoms. No child had a repetition of convulsions after its use.

It will be seen also that a marked increase in the Ca of the serum takes place so that we can measure the improvement that results. (Table III).

TABLE III.—TETANY. CALCIUM EXPRESSED AS MILLIGRAMS PER 100 C.C.

No.	Age.	Calcium.	Calcium after calcium treatment.
1	6 months	5.45	8.5
2	3½ years	5.8	
3	18 months	4.7	8.45
4	6 months	5.2	5.85
5	6 months	5.8	9.0
6	5 months	3.5	7.5
7	5 months	5.7	
8	8 months	6.0	
9	8 months	6.0	
10	18 months	7.3	
11	7 months	6.3	
12	2½ months	6.0	
13	13 months	5.0	
14	5 months	5.0	

It cannot be said that tetany may not return if the Ca is stopped. We usually have not interrupted its use. Certainly in our hands for the active symptoms it has been altogether the most satisfactory remedy.

DISCUSSION

Dr. Rowntree asked the author's views concerning alkalosis in these cases of tetany.

Dr. Koplik asked whether these cases when the calcium content of the blood was taken were dieting, especially whether they were on their usual diet they had been accustomed to or on some special diet.

Dr. Meltzer asked whether in those cases wherein the calcium content was diminished the magnesium was determined. He thought it possible that in these cases the magnesium content may be proportionately more diminished than the calcium content.

Dr. Wilson asked if Dr. Howland had determined the ammonium carbonate in the blood. It seemed in these cases hardly conceivable that the simple addition of calcium to the blood would directly influence tetany unless by the neutralization of some other substance. Had Dr. Howland any idea as to what this substance might be?

Dr. Howland (closing) said they had not determined the ammonia in the blood, a very difficult thing to do, and he believed it had never yet been satisfactorily accomplished in any considerable number of patients. It requires more blood than he and his associate cared to withdraw from an infant.

As to Dr. Meltzer's question in regard to the magnesium they preferred, as the paper stated, to defer consideration until some future time, though his impression was that the magnesium content was not very greatly altered.

Answering the question of Dr. Koplik, the children were on the same diet which they had been on for some time; no special diet was employed.

Answering Dr. Rowntree's question with regard to the alkalies, there was no demonstrable increase in the alkali reserve of these children.

A MODIFICATION IN METHOD OF PNEUMOTOMY FOR BRONCHIECTASIS

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AND

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Bronchiectasis is not a common disease, its incidence ranging from only 0.078 per cent. in American to 0.16 per cent. in European clinics. The postmortem statistics, however, show a greater incidence of 1.19 per cent. in America to 2 per cent. in foreign countries, figures which speak very strongly for the disease being frequently overlooked in the living subject.

TABLE SHOWING LOCATION OF BRONCHIECTATIC CAVITIES

	King[1] (69 cases), per cent.	Lebert[1] (54 cases), per cent.	Lord[1] (45 cases), per cent.
Bronchus (rarely affected) . .			
Single cavity	Not reported	Not reported	6.6
Confined to one lobe (multiple dilatations circumscribed) .	....	27.7	11.1
Confined to one lobe (multiple, diffuse)	....	Not reported	22.2
Unilateral (those due to lues, external pressure of tumors and foreign bodies, generally unilateral)	37.7[1]	52.0	Not reported
Tuberculous (upper lobe by predilection)			
Non-tuberculous (lower lobe by predilection)			

But though an affection rather rare, it is, nevertheless, a most loathsome and serious disease; so loathsome indeed as to cause its unfortunate victims to become actual social outcasts from the offensiveness of their sputum, and serious because exposed constantly to such dangerous complications as fatal hemorrhage, pneumonia, gangrene, putrid pleurisy, cerebral abscess, and meningitis.

The first difficulty in an effort to furnish aid to these terrible sufferers is encountered in the diagnosis of the malady. The history of long-continued cough and expectoration of large quantities of purulent sputum, generally offensive, are, of course, highly suggestive. Physical signs, however, and even *x*-ray findings, may give only the impression of either a localized pulmonic infiltration or pleural accumulation, or else signs of cavity formation, without furnishing any definite information of cavity formation occurring as dilatations in the bronchial tree. Any procedure, therefore, that may throw any additional light on this obscure question should certainly be welcomed.

A modern diagnostic aid that has proved of the greatest assistance is the bronchoscope, an instrument which is strongly championed by Yankbauer,[9] who claims with this instrument in bronchiectasis to distinguish endobronchially three groups of cases:

First: Dilatation of one or both main bronchi which can be distinctly recognized. In the other groups the main bronchi are not apt to be dilated. Secretion oozes into the main bronchi even after they have been just emptied, coming from the smaller tubes. These latter cases should be divided into the following classes:

1. When pus is seen to be coming from all the smaller bronchi on one or both sides.

2. When pus is seen to originate and to be coming from a single branch only; this latter group is, of course, the most favorable for operation.

Jackson,[3] among others, emphasizes the great importance of always seeking for foreign bodies as possible causes of bronchiectasis, even in the apparent absence of any history of such an accident, and accordingly he lays down the following rules:

Every case of pulmonary suppuration and chronic cough should have a skiagram no matter how certain the diagnosis.

Every case with a history of the swallowing of a foreign body should have a skiagram, even though a foreign body may not be opaque to the *x*-ray, and also be bronchoscoped as well, especially if the *x*-ray result be negative.

In all cases with a foreign-body history of a substance opaque to the *x*-ray a skiagram should be made to determine definitely the absence or the presence of a foreign body.

A condition of "drowned lung" or pus retained in normal bronchial tubes behind a foreign body may exist and result in bronchiectasis if not removed.

But when we come to the consideration of the treatment of bronchiectasis we realize to the fullest extent our limitations, for it is, we believe, generally conceded that all non-surgical therapeutic measures are rarely curative, and are therefore, as a rule, merely palliative. We shall have, from the curative stand-point, then to exclude at once all such measures as climate, inhalations, intratrachial injections, bronchoscopic treatment, internal medication, postural treatment, etc., at least in the management of focal forms of the disease which are favorable for surgical interference. And even when we come to consider surgical procedures in this class of cases, we shall find that we have to discard for the same reasons such methods as collapse therapy, which includes artificial pneumothorax and extrapleural compression with a plomb (Tuffier); ligation of pulmonary artery for production of pulmonary fibrosis, thoracoplasty, phrenicotomy, and even pneumotomy. The modern position taken is that pneumectomy or lobectomy is the only procedure that promises complete cure through total extirpation of the diseased areas; and the reason for this radical attitude of today is simply that it is not conceivable that the rigid walls of the bronchi in bronchiectatic cavities, embedded as they are, moreover, in sclerosed pulmonary tissue, could be made to collapse for the obliteration of suppurating cavities either through compression or drainage. The only possible exception to this rule may be the rarely occurring small single bronchiectatic cavity, with not too resistant walls, when pneumotomy with or without compression may be successful. Unfortunately, however, in the disease under consideration we have nearly always multiple dilatations with resistant walls and without necessarily any communication with one another, which therefore are not compressible, and when drainage of one pocket may occur without collapse of its walls and without any appreciable effect on the other cavities.

Even pneumectomy has also many limitations as regards selection of cases, ultimate results, and mortality. For according to Robinson:[5] "The case suitable for pneumectomy is a young adult

with a basal process confined to one lower lobe, with profuse sputum, offensive but not fetid; with loss of weight but without emaciation; with normal heart and kidney function. This is the type of individual in whom lung resection, properly executed, is attended with a good chance of cure. Not more than 1 in every 10 cases of bronchiectasis entering a hospital clinic represents this favorable type, the remaining 9 being unsuitable." So that nine-tenths of those afflicted with this terrible malady cannot avail themselves of such an extremely radical operation without multiplying many times the already markedly high operative mortality.

And as to the ultimate results of pneumectomy: The work of both Lilienthal[6] and Robinson[5] in this most difficult field of surgery has been both brilliant and praiseworthy, and doubtless at this date the recovery of some of the cases has been completed which at the time of reporting were not fully cured. For instance, in Lilienthal's group, reported July, 1916, the results are as follows:

Case I. Well since April 17, 1914.

Case V. Well since January, 1916.

Case II. Postoperative death.

Case VI. Postoperative death.

Case III. Well since May 4, 1915, but reopening of wound April 29, 1916, one year after apparent healing. Wound again about healed at time of reporting of case, but patient still in hospital.

Case IV. Well since May 18, 1915, but more a case of pulmonary abscess, with only a suggestion of slight dilatation of bronchial tubes.

So that on careful analysis we have here only two complete cures of bronchiectasis, and one of these is of only one year's duration.

In Robinson's[5] group, reported February, 1917, the results are as follows:

Case I. Plastic operation, twenty months after operation for closing of fistula, only partially successful. Death four years later from pneumonia.

Case II. Well nineteen months after operation.

Case IV. Disease still in upper lobe and also bronchial fistulæ still present four months after operation.

Case V. Patient discharged but wound as yet not perfectly healed; minute bronchial fistulæ still present two months after operation.

Case III. Death on fifteenth day after operation.

In the above group we have only one complete cure, so that in the combined statistics of 10 cases we have just three complete cures, or 30 per cent., who have experienced entire relief of symptoms with fully healed wounds. Of course it must be granted that a patient whose distressing symptoms of cough and foul expectoration are controlled should be practically considered cured even though he still have a bronchial fistula remaining.

It is likewise true that a risk of 30 per cent. mortality may not be considered prohibitive when a disease which so threatens life and wrecks health and happiness is under consideration.

Robinson's mortality in this group is 30 per cent. The mortality of several operators is as follows:

	Operative mortality, per cent.
Körte[4]	73
Sauerbruck[8] (123 collected cases)	35
Myer[7] (pneumotomy up to 1914)	50
Lilienthal[6] (pneumotomy, intercostal, 5 cases of bronchiectasis)	40
Robinson[5] (pneumotomy on 2 cases still living) general mortality	80

The following case, which, in conjunction with Dr. Mudd, has been under observation and study, is reported as presenting highly suggestive data from the stand-points of both diagnosis and treatment of bronchiectasis:

Mrs. E. T., married, aged fifty-six years, housewife, was referred to our service at St. Luke's Hospital. Family history negative. Previous health always good until onset of child-bearing period, after which she underwent several minor gynecological operations. Menstrual life normal. Seven living healthy children; three miscarriages.

Tumor removed from breast in 1901 by Dr. Franklin Martin, of Chicago, and pronounced non-malignant. Appendicitis in 1908; very ill for six to eight weeks; recovery without operation. No drugs or stimulants.

Present trouble began in winter of 1913 with what she was told was "laryngitis." Cough gradually increased in severity, becoming later most distressing, but without expectoration, and has continued ever since with remissions during the summer.

March, 1916, all her symptoms increased markedly in severity, with fever, and then for the first time did sputum appear, copious, of a dull gray color; never offensive, at times bloody or pure blood. On one occasion she raised a Y-shaped cast of a bronchus about the "color and consistency of liver," after which she remained in a stupor for two and one-half hours, so terrific was the straining effort of the cough. Temperature at this time ranged from 99° in the morning to 103° or 104° in evening.

Physical examination at the time of coming under our observation, April 28, 1916, showed complete dulness, with diminished breathing and pleural friction over the area on the right side of the chest posteriorly extending from the seventh rib downward and from the median line for-

FIG. 1.—Taken just prior to May 1, 1916. Showing shadows of area of infiltration in the right lung about bronchiectatic cavities.

ward for a distance of 14 cm., with a point of tenderness midway between the posterior median line and the anterior boundary of this space, and in ninth intercostal space. Chest and abdomen otherwise negative, signs which spoke either for localized fluid collection or thickened pleura. No cavity findings. Skiagram was corroborative. Six examinations of sputum showed many streptococci and pneumococci but no tubercle bacilli. Red cell count and hemoglobin about normal. A polymorphonuclear leukocytosis of about 12,000 was present. Urine showed occasionally a trace of albumin with at times a few hyaline casts. No sugar. Wassermann negative.

May 1, an effort was made to obtain pus with exploring needle, but only what seemed to be a small amount of old blood clot was obtained.

May 3, second operation under ether revealed a small amount of pus, whereupon three inches of the eighth rib was resected and a small cavity located at the end of the exploring needle, from which masses of thickened pus, together with a mass suggestive of new growth, was removed. The report on this tissue made by the pathologist to the hospital was that the process was inflammatory and non-malignant.

June 24, there being no definite improvement in the symptoms under ether, four or five inches more of the eighth rib were removed anteriorly and also all the reformed portion of the rib posteriorly nearly to the spinal column; six inches of the ninth rib was also resected, establishing a window in the chest wall $2\frac{1}{2}$ x 4 inches in dimension and affording a distinct view

FIG. 2.—Exploration with resection of eighth rib made May 3, 1916, revealing a small pus cavity.

of the involved lung, which was found completely adherent at every point, but no new purulent focus could be discovered. The wound was packed wide open.

December 13, patient returning with no decrease in her harassing symptoms, and with a persisting sinus, which had developed in the interim, sinus was injected with bismuth, with the hope of getting some information in the subsequently taken skiagram of the direction and extent of the cavity or cavities, and in this effort we were rewarded with a clear view of the numerous bronchial dilatations, their situation and size as clearly outlined in the stereoscopic picture. In this way our appreciation of the conditions we had to deal with was greatly enhanced. We saw then clearly that we

must plan to attack a multiple circumscribed bronchiectasis. Pneumectomy was, of course, at that time considered, and in fact when arranging for the

FIG. 3.—Injection December 13, 1916, of pulmonary sinus through chest wall with bismuth. Showing clearly the outline of several bronchiectatic cavities.

FIG. 4.—Taken May 27, 1917. Showing disappearance of bronchiectatic cavities and marked clearing up of involved area in the right lung.

next operation on December 18, 1916, we had prepared for the more radical operation. We finally concluded to explore again the wound under the new light obtained by the skiagram of the bismuth-injected wound. Two sinuses were found leading to saccular dilatations of bronchial tubes containing pus. It was further decided to try the effect of the cautery knife in the incising of these sinuses, and for the following reasons: (1) for the control of hemorrhage; (2) for the thorough destruction of pyogenic membrane; (3) for the complete obliteration of the walls of the involved bronchial tubes, thereby permitting the collapse of the walls of the sinus and favoring of the healing process. Accordingly the lower of the two sinuses was first deeply plowed through and then the upper, but it was found necessary to stop before the bottom of the latter was reached on account of severe bleeding from a large vein which, however, was readily controlled by firm gauze packing. For the first time our efforts showed any evidence of success in the control of our patient's distressing cough, as there was almost immediately a decided improvement not only in the cough but also in the amount of expectoration. The wound also looked healthier and discharged less.

In observing the involved lung, however, through the large window in the chest wall, pus could be still seen oozing from the ends of other dilated tubes, and so on December 23 we decided on further cauterization; and the absence of pulmonary pain sensation, being recalled by the tolerance the patient manifested to the exploration with the probe, we attempted the cauterization without general anesthesia, and were able to cauterize two more sinuses, with the aid of only $\frac{1}{3}$ grain morphin and $\frac{1}{150}$ grain atropin given about one-half hour in advance, the patient declaring that she experienced no pain at all, the only disturbance felt being the consciousness of the odor of her own flesh burning. Two of the sinuses were burnt so deeply into the lung that the impulse of the heart was transmitted to the cautery blade. While burning the third sinus hemorrhage again forced us to stop, though the bleeding this time at last was quickly controlled by firm gauze packing.

Similar locating of sinuses and pus pockets through observing pus ejected from the open ends of the bronchial tubes and the destruction of these sinuses with the cautery knife, with $\frac{1}{2}$ grain morphin as only anesthetic, was practised on December 30, 1916, and February 2, February 26, and April 13, 1917. During all of these treatments the patient suffered no pain so long as the cautery knife was working in the lung tissue, except at times a strange, easily borne pain referred to the upper abdomen, and curiously enough the same sort of pain the patient had frequently complained of at times long before any of the cautery operations had been performed.

The improvement in the symptoms of cough, expectoration, and pain noted after the first cauterization December 18, 1916, continued without

each subsequent cautery operation until they ceased entirely, and never have returned since the cautery operation on February 26, 1917.

The skiagram of March 27, 1917, shows an entire disappearance of the numerous bronchiectatic cavities before visible, together with a very marked clearing up of the infiltration of the lung in the involved area. And hand-in-hand with these evidences of definite improvement in the symptoms and physical findings there has been also a great gain in the patient's general condition, physical and moral. She was soon after the first cauterization able to gradually break away from opium preparations to which she had been driven by intolerable pain, harassing cough, and expectoration. She promptly left her bed to be up and around the hospital. Appetite and sleep have been gradually returning with a corresponding gain in weight. Her general morale has also greatly improved, and, as she now expresses it, she feels "like another woman in every way." Her condition, in fact, is today an exact counterpart of some of the cures through pneumectomy, viz., she is symptomless as regards her old bronchiectatic cough, expectoration, fever, and pain, but she still has two, perhaps three, small bronchial fistulæ remaining which give her no trouble at all, and which we feel certain will soon be entirely healed with one or two more cauterizations.

Appreciating fully, of course, the importance of making every allowance for deductions based on a single case, and that case, too, without as yet a completely healed wound, still, in conclusion, we wish to offer the following suggestive impressions gleaned from observation and study of our patient.

1. Given a fistulous opening through the chest wall into lungs, injection of sinus with bismuth prior to taking of skiagram may furnish most valuable information, not only of the presence of bronchiectatic cavities, provided, of course, that cavities communicate with the sinus, but also of their size, extent, and location, thereby greatly facilitating their management.

2. Establishment of a large window in the chest wall in this class of cases, together with the already adherent or made adherent lung, affords an opportunity when combined, if possible, with the bismuth injection for observation and study of the field of disease, whereby the various sinuses and pus pockets may be successfully located and followed and destroyed ultimately in their entirety, such thorough destruction of pyogenic membranes and bronchial walls enabling sinus and cavity to collapse and heal.

3. Under the above conditions the galvanocautery used freely in the ploughing up of sinuses and cavities may afford a safe and effective method of cure of bronchiectatic symptoms, avoiding thereby the dangerous shock of pneumectomy.

4. With the operative field in the lung tissue made accessible through a large window in the thoracic wall, the cautery knife may be used with morphin hypodermically as the only anesthetic, thereby eliminating the great dangers of pus inhalation in general anesthesia.

5. Thus the limitations of usefulness of the method as described should not be nearly so great as those of pneumectomy because devoid entirely of the two greatest elements of danger in lung resection, viz., general anesthesia and shock. The cases need not therefore be so rigidly selected.

July 31, 1917. Since May, 1917, the patient has had neither cough nor expectoration. Through cauterization, without general anesthesia (except at one séance when we were obliged to work near a large nerve trunk), the three or four bronchial fistulæ have been closed and the wound is almost entirely healed. Marked improvement in patient's general condition.

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THE DISTRIBUTION OF BILE IN CERTAIN TYPES OF JAUNDICE

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In a previous publication from this clinic[1] is was proposed by the writer to examine the blood for bile in cases of jaundice, and a scheme was devised to make measurements on blood, stool, and urine which when correlated with the color of the skin might throw some light on the role of bile in the various types of jaundice. The work covered by this report is the examination of 395 specimens of blood plasma, together with an examination of the urine and skin, and in a lesser number an examination of stool and duodenal contents according to that scheme. The methods employed are essentially those previously described, but with the following modifications: A tintometer constructed in the laboratory is now used to measure the color of the plasma, and readings can be made more accurately than by our earlier method, when test-tubes are simply held parallel and observed down the length of the tube. The color of the plasma is taken as an index of the bilirubin content and the amount is expressed by a number corresponding to the number of times the plasma must be diluted to reduce the color to a tint that can just be discerned in a column 1 cm. deep.

The writer is of the same opinion as formerly expressed, that the yellow color of plasma is due solely to bilirubin, and that the Gmelin test with nitric acid can be used to test for it. To substantiate this claim the writer made parallel tests in 239 cases, using the Gmelin and Huppert-Cole tests. The results were identical in 224 cases, contradicting in 15. In 3 the Huppert-Cole was positive while the HNO_3 negative. In 12 the HNO_3 was positive and the Huppert-Cole

[1] Dissociated Jaundice, Arch. of Int. Med., 1916, xviii, 289.

negative. But the value of the Huppert-Cole tests depends to a certain extent on the quantity of plasma used, and it is sometimes negative because not enough plasma is available. This slight discrepancy is certainly explainable by the difference in delicacy of the tests and does not disapprove at all the identity of the substance tested for.

The test for bile salts in the blood is modified, so that we may now dialyze 3 c.c. of plasma in 9 c.c. of water through collodion sacs, where formerly we dialyzed 5 c.c. into 10 c.c. of water and alcohol. For cholesterol in the blood the writer has found no satisfactory and practicable method.

Bile Pigment. 395 specimens of blood plasma were examined in this manner. Of this number 75 were described as colorless, that is, there was no distinct yellow color present, there being only a faint turbidity or a faint pink or buff tint distinguishing the specimen from water. This group of 75 all gave negative results when tested chemically for bilirubin. 222 specimens were distinctly yellow and gave a chemical test for bilirubin. The specimens of this group measured from 15 to 375. Forty represents the critical point at which the cholemia becomes a visible jaundice. Of the 222 specimens, only 2 were over forty without the patient being jaundiced, and but 10 were under forty with the patient jaundiced.

Between the 75 specimens and the 222 giving a chemical test for bilirubin were 94 specimens that were distinctly yellow in color, but gave no chemical test for bilirubin. It is in this group that the possibility of the presence of some yellow substance other than bilirubin must be seriously considered. In this group was the blood from 10 primary anemia patients, from 7 patients who had been jaundiced previously, from 11 with acute infectious diseases in which jaundice is very common, from 6 with some disease of the liver or gall ducts—that is, 34, or about one-third, in which bilirubin is very commonly found. In some of them biliburin had actually been found previously and in others it was found subsequently. Inferentially we can say that bilirubin was present in one-third of all these, but in amounts too small to be detected chemically. The remaining two-thirds were all from normal individuals, or patients admitted to the hospital for some condition not associated with jaundice. In

all this class of doubtful, subicteric plasmas at no time was there ever present any pigment in large amounts. The writer has repeatedly tested those specimens for lutein and urobilin, which are supposed to pigment the plasma at times, but in this group neither of these was found; and since we very commonly find that bilirubin occurs in amounts large enough to be tested chemically in perfectly normal individuals, it is safe to assume that bilirubin is the pigment in this entire group of 94.

By an analysis of the 220 specimens of blood plasma that contained bilirubin in amounts large enough to give a chemical test, considerable light is thrown upon the behavior of bilirubin *per se*. This has aided distinctly in the interpretaton of the various findings in particular groups of cases and somewhat in the interpretation of individual cases. As indicated above, the degree of staining of the plasma varied from 15 to 375, and 40 represents the critical point where the cholemia becomes jaundice; 100 represents a distinct jaundice; 300 and over a marked jaundice. The series does not contain a case of that very extreme jaundice sometimes seen in prolonged complete biliary obstruction. 141 of the 222 were from jaundiced patients; 81 were from patients not jaundiced. In the group of 81 are 14 from normal patients; 20 from patients admitted for conditions in no way associated with jaundice. The writer frequently finds blood plasma very distinctly stained with bilirubin, where there is absolutely no explanation, unless it be that a relative degree of cholemia is normal. A goodly number of these cases were investigated repeatedly and the findings confirmed, but no individual or physiological variation can be described as yet. On the other hand, the degree of cholemia was frequently found distinctly above forty, the critical point, where jaundice should be expected, yet none could be observed by the ward physicians; 3 were found at fifty or over.

Of the 395 examinations made it was found in 7 cases that the patient was described as jaundiced, but the plasma was found absolutely colorless. This at first suggests jaundice without cholemia, but 6 out of 7 cases were patients with a very severe secondary anemia, in which the normal pigmentation is exaggerated by pallor and the condition simulated jaundice; the remaining 1 was described

as doubtful. We thus dismiss from this report jaundice without demonstrable cholemia.

The writer has found that a distinctly higher degree of cholemia can exist without choluria, and 60 is found to express the critical point for choluria or the average above which cholemia becomes choluria. There is, however, a very wide range in the degree of cholemia without choluria, so much so that when some of the more certain factors concerned in the behavior of bilirubin in the blood are determined this disparity may be of much diagnostic importance. 153 out of 220 specimens showed a chemical test for bilirubin in the plasma without choluria. These ranged from 15 to 275. In many cases this retention of bilirubin was associated with impaired kidney function. In other cases no other retention could be demonstrated and there was no reason to expect any impairment of kidney function. The duration of the jaundice as well as the intensity seem to be factors in determining this disparity. In general a more prolonged and a more severe jaundice is associated with a high cholemia when there may be no choluria. Also when there is disease of the liver with change in its size and consistency this disparity is frequently marked. In diseases of the bile ducts the disparity is less frequent and less marked. Choluria without cholemia was not seen; also choluria without jaundice in so far as bilirubin alone is concerned, has not been observed.

From the foregoing analysis of 220 cases in which bilirubin was found chemically the writer is impressed with the following points in the behavior of bilirubin in the blood: that bilirubin is very commonly present in the blood of normal individuals in varying amounts; that it is usually readily diffused through the lymph into the skin, but less readily through the kidney; that it may be fixed in the blood and thus withheld from lymph and urine; that it is not formed or retained in the lymph in higher concentration than in the blood; that it never appears in the urine without reaching and maintaining a certain concentration in the blood.

Bile Salts. In studying the bile salts in the blood the writer has thus far found no satisfactory quantitative method. Further studies on the dialysis of blood plasma through collodion into water confirms the belief that cholesterin and lecithin are not so

dialyzed, and that the Pettenkofer test on the dialysate together with the spectrum is a specific test for bile salts. It is not yet possible to bring much order out of the chaotic findings that appear in investigating bile salts, and until a quantitative method is used and a more satisfactory method is found for the urine very little can be said with assurance about the behavior of bile salts in the blood. A brief analysis of some of the results alone is justifiable.

Out of 395 specimens examined bile salts were found in 124. In 87 cases bile salts occurred in the blood in conjunction with bilirubin. This occurs most commonly when bilirubin is highly concentrated in the blood and when both bile salts and bilirubin are present in the urine.

In 37 cases bile salts occurred alone. This was most often in cases of primary anemia, acute infectious diseases, diseases of the liver in which there is change in the size and consistency of the liver, and in nephritis.

In 10 cases bile salts were found in conditions never associated with jaundice. In 4 cases bile salts were found in normal individuals. When larger amounts of plasma are dialyzed bile salts are very often found in normal blood, and it is the impression of the writer that if 15 c.c. of plasma are dialyzed by the method described and all the dialysate be concentrated into 2 c.c. the Pettenkofer test will be uniformely positive in normal individuals. In 106 cases bile salts were found in the blood and not in the urine; in 13 bile salts were in the urine and not in the blood. This disparity between cholemia and choluria of salts, with a very small number showing salts in the urine and none in the blood, but a large number with salts in the blood and none in the urine, suggests a process of retention; whether this is due to a fixation in the blood or a diminished permeability of the kidney is not yet clear. More accurate methods for examining the urine and a quantitative study of the blood are necessary to clear this up.

Urobilin. 133 specimens of blood were examined for urobilin and 22 found positive. This rather large number was at first surprising after the consistently negative results which we have previously reported and which other observers report. The method used is the same as used previously, viz., the plasma is centrifuged

with an equal volume of 90 per cent. alcohol saturated with zinc acetate and Ehrlich's aldehyde reagent added to the clear liquid. Both the purple red color and the spectrum were found in every positive test. The positive results are attributed to the selection of the patients and the time of taking the specimens.

Of the 22 positive cases, in 18 urobilin occurred in conjunction with bilirubin, and in 9 cases it was found where no jaundice was observed. In 3 instances urobilin was found in large amounts in the plasma of patients that were not jaundiced, and, moreover, the plasma itself was practically colorless.

The urine was examined in 325 cases and urobilin found 110 times. In 88 cases there was urobilin in the urine with none in the blood. In no instance was there urobilin in the blood, with none in in the urine. In but 2 of the patients in whom a urobilinemia was found was there any distinct impairment of the kidney. In every case in which there was urobilinemia enormous amounts were also found in the urine. It is therefore quite obvious that there is no retention of urobilin in the blood. Urobilin dialyzes very promptly into water through collodion membranes and leaves a perfectly clear and colorless dialysate; it can then be found in the dialysate by the Ehrlich aldehyde reagent and the spectroscope. From the foregoing observation we can say that urobilin is frequently found in the blood in large amounts without causing jaundice; that it is very promptly yielded to the kidney; and that it does not occur in the blood unless it is formed in excessive amounts.

We have over 1000 quantitative estimates of urobilin in stool and urine, according to the methods of Wilbur and Addis,[1] but the writer does not feel that this has contributed anything to the general information on the distribution or behavior of bile. The difficulties due to irregularities in the formation and elimination of stool, catharsis, etc., have not yet been overcome, otherwise the method is enitrely successful.

In examination of the urine the methods used are the same as previously reported. No extensive use has been made of the quantitative method for bilirubin as described by Whipple.[2]

Although it has worked quite satisfactorily in deeply pigmented

[1] Arch. of Int. Med., 1914, xiii, 235. [2] Ibid., 1916, xviii, 289.

plasmas and urines, when smaller amounts of pigment are present the writer has difficulty in getting readable colors.

In a previous publication by Dr. Hoover and the writer[1] dissociate jaundice was elaborated and some of its terms defined. In the present report little can be added to the general premises of that work, especially anything on the significance of dissociation itself. In considering the various groups of cases separately the dissociation begins to take some form and meaning. Practically every case of jaundice, if the urine and blood be followed carefully through the onset and disappearance of the jaundice, will present dissociation at some time or other.

Laennec's Cirrhosis. The writer observed 18 cases of Laennec's cirrhosis with alteration in size and consistency of the liver, chiefly the small, contracted liver. Some of the cases had ascites. 37 observations were made; bilirubinemia was found in 31 instances, and in all the 31 cases there was jaundice. The bilirubinemia varied from 20 to 350. Bilirubin was found in the urine of 17, but there was a marked disparity between cholemia and choluria; 6 plasmas were found at sixty or over without choluria; bilirubin was not withheld from the lymph, but was not always freely yielded to the kidney. In none of these cases was there any great impairment of kidney function, so the bilirubin is probably fixed to the plasma. In the cases in which the jaundice had been the most prolonged was this fixation most marked; the severity of the systemic symptoms were never an index to the fixation. Bile salts were found in the blood in 10 cases; in the urine in 12. There seems to be no retention of the salts in the blood.

There is in this group a very common and mystifying dissociation of the biliary elements in both blood and urine, from which the observer has gathered nothing but confusion.

In 2 cases there was at one time a marked increase in the bile output found in the stool, associated with a marked jaundice and a deep choluria, showing that the formation of bile pigment had been increased.

In 3 cases there was a very marked diminution of the output of bile in the stool simultaneously with a want of bile in the urine and a

[1] Arch. of Int. Med., 1916, xviii, 289.

very moderate jaundice, showing a definite diminution of the formation of bile. In 5 there was a distinct diminution of bile in the stool at a time when the blood, urine, and skin were deeply stained, thus showing that obstruction to the drainage of bile sometimes occurs. Several cases went through a period of jaundice and ascites without showing any demonstrable change in the daily output of bile in the stool.

Hanot's Cirrhosis. 3 cases of Hanot's cirrhosis were examined, but very little disturbance in the formation or distribution of bile could be found—a thing quite surprising considering the alteration in the size and consistency of the liver and the general symptoms. The same can be said of 3 cases of syphilitic disease of the liver, except of 1 in which there was great deformity about the hilus of the liver, as shown at autopsy, with obstruction of the ducts.

Obstructive Jaundice. 19 cases of obstruction of the bile ducts were observed and 23 specimens of blood taken. 23 specimens contained bilirubin, most of them over 100. All were jaundiced and all except 2 were accompanied by bilirubin in the urine. In this group there is very little disparity between cholemia and choluria, but inasmuch as there is a higher average cholemia than in the cirrhosis group, that point in difference is of little value. In 12 out of 23 plasmas bile salts also were found. In the urine, too, bile salts and bilirubin were very seldom dissociated in this group. This consistency between bile pigment and bile salts in both blood and urine in obstructive jaundice, especially at the onset, or while the process is progressing, is regarded by the writer as characteristic of obstructive lesions. Very few exceptions to this have been found that cannot be explained by some complication, such as septicemia, nephritis, etc. After the obstruction is relieved the bile salts disappear from the urine and blood first, and we then have, of course, a dissociation, but the dissociation is of renal origin. The early obstructive lesions are the best and most common examples of the so-called "complete icterus"—that is, bilirubin and bile salts in both urine and blood. The stool in obstructive jaundice varies in its bile content according to the extent and duration of the obstruction. That the bilirubin content of the blood and urine must necessarily become greater as the amount in the stool diminishes is not true.

The writer observed 3 cases in which the stools were acholic for over a week, during which time the jaundice remained the same, and the same amount of bilirubin was given off each day by the urine; apparently the formation of bile had been diminished by the obstruction to an amount that could be eliminated by the kidney as fast as it was formed. In all these 3 cases there was no way of estimating the condition of the portal blood flow, so that it is not certain that biliary obstruction alone was the inhibiting factor.

One case has been observed, including an autopsy in which no lesion save obstruction could be found, yet the patient went six days with only a very slight increase in the cholemia and jaundice. The writer is of the opinion that under some circumstances obstruction alone will inhibit the formation of bile.

Sixteen cases were investigated in which a diagnosis of cholelithiasis was made, but in which no obstruction could be proved; 7 of the plasmas contained bilirubin and 3 bile salts, and that only in very small amounts. None of the patients were jaundiced and none had bile in the urine (neither pigment or salts). Seven of these patients were operated, and in 3 gall-stones were found; but of this 3 only 1 showed cholemia before the operation, while of the 4 which had no gall-stones at operation 3 had shown cholemia before the operation. The examination of the blood for small amounts of bile has thus far been of no aid in the diagnosis of gall-stones that are producing no obstruction.

Catarrhal Jaundice. 7 cases of catarrhal jaundice were examined and 9 specimens of blood taken. Bilirubin was found in all; bile salts in 4. The distribution and behavior of the bile resembled obstructive jaundice in this respect: there was little dissociation of the pigments and salts in both blood and urine except after the process began to subside. There was also an intestinal hypocholia. Unlike most obstructive lesions there was frequently urobilin in the urine.

Chronic Passive Congestion. 12 cases of heart disease with chronic passive congestion of the liver were examined; most of them while decompensated. Bilirubin was present in 10 cases; bile salts in 3. Only small amounts of bilirubin were found, and but 2 of the patients were jaundiced and only 1 had bile in the urine. There was

considerable dissociation in the blood. Like Hanot's cirrhosis there is little change in the distribution of the bile pigment in proportion to liver changes.

Septicemia. 13 patients with septicemia were investigated, including 3 cases of typhoid, 5 of streptococcus, and 4 of colon infections. In 10 there was bilirubin in the plasma and 5 bile salts; 6 had large amounts and were deeply jaundiced, but only 2 of the 6 had bile salts in the blood. On account of the liability to so many complications, especially nephritic, it is impossible to generalize in this small group.

Pneumonia. 40 cases of pneumonia were investigated and 48 specimens examined: 30 specimens contained bilirubin, averaging 50; 14 contained bile salts; 12 patients were jaundiced and 6 had bile in the urine, the maximum being 100; 19 contained urobilin in the blood and 39 in the urine. It is this group that provided the large number of specimens with urobilin in the blood, but only in those cases in which the specimen was taken early in the course is the urobilin found. Urobilin was found to appear in the blood very early in the course of the disease—in several instances preceding jaundice. It also disappears very rapidly, disappearing from the blood several days to a week before it is absent from the urine. In but 4 instances was urobilin found on two successive days. The severity of the infection was not an apparent factor on two successive days. The severity of the infection was not an apparent factor in the presence of urobilinemia: out of 15 patients who showed it 10 recovered.

Examination of the stool in pneumonia cases showed an increase in bile output for several days—usually during the period of urobilinemia or jaundice.

Malaria. 5 cases of malaria were examined and 6 specimens taken; 5 out of 6 contained bilirubin, and none contained bile salts. The absence of bile salts is significant, but the numbers are too small to justify much speculation. The output of bile in the stool in 3 of this group was increased; in the other 2 no measurements were taken.

Ectopic Pregnancy. 3 cases of ectopic pregnancy were found and 4 specimens examined. Bilirubin was found in all 4 specimens,

but only in small amounts; none of the patients were jaundiced. Bile salts were present in but 1. The stools showed no increase in bile output.

Teniasis. 3 cases of Dibothricephalus teniasis were found and 4 specimens examined. Bilirubinemia was present in all, but only 1 patient was jaundiced. Bile salts were present in the plasma of 2 out of the 3 patients. In all 3 the stools showed an increase in bile. This group cannot be distinguished from primary anemia by the behavior and distribution of bile.

Plumbism. 4 cases of chronic lead-poisoning were found and 3 had bilirubin in the plasma, but all 4 had bile salts in the plasma. Bilirubin was present in small amounts and none of the group of patients was jaundiced. The urine in all was negative; the stools also. The presence of bile salts in this group may be of some importance.

Primary Anemia. 34 cases of primary anemia were examined and 42 specimens taken; 32 specimens of plasma contained bilirubin and 13 of the patients were jaundiced. Bilirubin was not found in the urine of any. The bilirubin in the blood in 10 specimens was 50 or over. Bile salts were found in 24 plasmas and in 2 urines. Urobilin was found in 20 urines; the stools showed increase in bile output in all that were satisfactorily investigated. This group is characterized by a particularly high degree of cholemia without jaundice or choluria and by a marked retention of bile salts in the blood. This is essentially the same as previously reported. Recently it has been found that in primary anemia there is a marked impairment of kidney function and the possibility of the choluria in primary anemia being due to renal impairment must be considered. We therefore examined the plasma of 16 nephritics to determine somewhat the role of renal impairment in the accumulation of bile in the blood. These plasmas are uncommonly clear and colorless. Only 2 contained bilirubin, 1 at five and 1 at ten. This in some cases can be explained by the retention of water in the plasma; 7 specimens contained bile salts. None of the patients were jaundiced, and the urine in all was negative. It is quite significant that 7 patients without apparent cause had increased amounts of bile salts in the blood, and it is very probable that the renal impairment in primary

anemia is an important factor in the accumulation of the salts in the blood.

Secondary Anemia. 7 cases of severe secondary anemia were examined. The plasma in 6 contained very small amounts of bilirubin, but none contained bile salts. Four of these patients were thought to be jaundiced, but this is explained by the great pallor. The urine of all was negative; the stools of all this group that were satisfactorily investigated showed a slight diminution of bile output. This fact is significant only when we compare this group with the primary anemias due to dibothriocephalus.

The plasma of 22 perfectly normal individuals was examined, and 34 specimens taken; 8 specimens contained bilirubin and 4 bile salts. The urine in all was negative. In connection with Dr. Christie, who has examined the blood recently of many normal individuals, in his work on renal functions, an opportunity was given the writer to obtain a limited number of specimens at intervals during the day, in relation to taking food and abstaining from food, but thus far the meterial is too limited to be of value, except that nothing radically contradictory has been found.

EXPERIMENTAL LESIONS IN THE CERVICAL SYMPATHETIC GANGLIA IN RELATION TO EXOPHTHALMIC GOITER

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That exophthalmic goiter, the clinical manifestations of which are due essentially to a greatly increased protein metabolism, is the joint result of disturbance in the several glands concerned with metabolism there can be little doubt. The fact that the thyroid shows a pronounced and constant series of functional changes parallel with the course of the disease, and the further fact that removal of the gland arrests the symptoms, is convincing though not absolute proof that the thyroid is the secretory gland the hyperfunction of which initiates the metabolic disturbance.

But is the primary hyperfunction of the thyroid the result of primary pathological change within the gland itself or of direct stimulation from its nerve supply? Cannon's[1] experimental production in cats of some of the symptoms of exophthalmic goiter by continuous stimulation of the thyroid through the sympathetic system suggests the latter. Durante and I[2] have shown that in all cases of exophthalmic goiter we have had an opportunity to examine there is a pronounced and constant pathological lesion in the cervical sympathetic ganglia from which the thyroid receives its entire nerve supply. There is much suggestive evidence that these pathological changes in the cervical sympathetic ganglia are the result of direct bacterial infection within the ganglia.

The object of the present series of experiments has been to determine the effect directly upon the cervical sympathetic ganglia and indirectly upon the thyroid of various forms of stimulation applied

to the ganglia themselves in healthy animals. Goats have been used for the experiments almost exclusively, and the results on these animals only will be described herein. The goat is a very desirable animal for experiments on the sympathetic ganglia and the thyroid, since the tissue elements of both these organs in their normal and pathological morphology and their staining reactions closely resemble those of the tissue elements of the same organs in man.

Stimulation in some of the experiments has been produced by electricity; in most instances, however, the stimulus has been obtained by direct bacterial inoculation into the ganglia. Observations have been completed on nineteen goats, and are still in progress on six others.

Technic. *Electric Stimulation.* After proper etherization of a goat, its right superior cervical sympathetic ganglion was exposed. The ganglion was then directly stimulated by a moderate tetanizing current for one second at intervals of three seconds for a period of one hour. During the experiment the animal's blood-pressure was taken and the amount of saliva excreted noted. After one hour the right cervical ganglion and the right lobe of the thyroid were removed with as little loss of blood as possible. The left superior cervical sympathetic ganglion was then exposed and stimulated in the same manner as the right had been but for a period of five and one-half hours. At the end of five and one-half hours the left superior cervical sympathetic ganglion and the left lobe of the thyroid were removed. After removal the ganglia and the lobes of the thyroids were properly fixed and stained by various methods, the ganglia usually by Nissl's and Ramon y Cajal's methods and the thyroid with hematoxylin-eosin and by Bensley's acid-fuchsin-methylene-green after acetic-osmic-bichromate fixation.

Bacterial Stimulation. After properly etherizing a goat, its right or left superior cervical sympathetic ganglion was exposed and a small quantity of a culture of some bacterium was injected into the capsule of the ganglion. The wound was closed with aseptic precautions and the goat placed under observation. The period of observation varied from three days to three months. A few of the animals died, and in such instances complete postmortems were made. In some of the others the cervical sympathetic ganglia

and the lobes of the thyroid from both sides were removed at operations. In the remainder of the goats only the injected ganglion and the thyroid lobe on the same side were removed and examined.

Summary of Observations. 1. The normal nerve cells of the cervical sympathetic ganglia in the adult goat closely resemble the normal nerve cells of the cervical sympathetic ganglia of the human adult except that a relatively large number of them are binucleate. Similarly, the thyroids of the adult goat when at rest histologically closely resembles the resting adult human thyroid.

2. (*a*) Moderate electrical stimulation applied for one second at intervals of three seconds for a period of one hour to the superior cervical sympathetic ganglion of an adult goat appears to produce no marked changes in the blood-pressure or respiration. If there were any definite changes, they were masked by the diffuse stimulation involving the vagus. There was marked salivation.

(*b*) Microscopically after the electrical stimulation noted above a large number of the nerve cells of the stimulated ganglion were swollen and showed hyperchromatization. The demonstration of dissolution of the chromatin by Nissl's method and of the presence of lipoid changes by Sudan III and Ramon y Cajal's methods has not been possible in any of the cells.

(*c*) After the above-mentioned stimulation, the cells of the thyroid parenchyma were found swollen, their protoplasm distinctly granular and their nuclei well rounded. The acini were distended with a feebly staining colloid secretion, the numerous large vacuoles in stained preparations of which indicated the liquid character of the secretion. The condition of the cells and colloid secretion was parallel in all respects to that found in the thyroids of early cases of exophthalmic goiter in the human subject.

3. (*a*) Moderate electrical stimulation applied to the superior cervical sympathetic ganglion for one second at intervals of three seconds throughout a period of five and one-half hours produced clinical changes similar to those noted in paragraph 2.

(*b*) Microscopically, after the electrical stimulation noted above, many of the nerve cells were markedly swollen and showed intense hyperchromatization. Many were swollen, hydropic and with disseminated chromatin. Sudan III preparations, even when thor-

oughly differentiated, showed conclusive evidence of lipoid change. This was demonstrated by Ramon y Cajal's method.

(*c*) After the above-mentioned stimulation, the cells of the thyroid parenchyma were found swollen but not nearly so much so as in those thyroids in which stimulation had been applied for only one hour. The protoplasm was clear and the nuclei showed a tendency to crenation. The acini were usually more distended and were filled with colloid material which was more densely stained and contained fewer vacuoles than that noted in paragraph 2-*b*. These changes were evidently the result of beginning exhaustion of the cells and resembled the changes in the thyroid in cases of exophthalmic goiter in the human subject in which remission of symptoms has already begun.

4. (*a*) After the injection of a virulent culture of Streptococcus hemolyticus into the capsule of the superior cervical sympathetic ganglion of goats the animals died within three days after exhibiting symptoms of intense toxemia.

(*b*) Within the injected ganglion of such a goat the nerve cells were found to lie in greatly distended pericellular lymph spaces. They were markedly hyperchromatic and hydropic, with diffuse dissemination of the chromatin or were more or less completely disintegrated. No evidence of lipoid change was demonstrated by the Sudan III or silver-impregnation methods.

(*c*) After the above injection, the cells of the thyroid parenchyma were palely staining, not swollen and apparently not overfunctioning. The amount and character of the colloid within the acini was not distinguishable from normal.

5. (*a*) After the injection of certain strains of Bacillus influenzæ of apparently low virulence, no systemic reaction of histological lesions were demonstrated. After the injection of other strains more recently isolated a marked inflammatory reaction was found around the injected ganglia, though the goats had shown no symptoms. Changes within the ganglia and within the thyroid were indistinguishable from those within the ganglia and thyroids from the goats described in paragraph 6.

6. (*a*) The injection of freshly isolated virulent cultures of Bacillus bronchisepticus into the superior cervical sympathetic

ganglion of adult goats usually produced marked constitutional symptoms such as trembling, increase of temperature, and loss of appetite, and frequently caused death in from three days to three weeks. No exophthalmos was noted.

(*b*) Within the injected ganglion of such a goat many of the nerve cells in animals dying early were found to be markedly hyperchromatic; others were hydropic with disseminated or invisible chromatin and more or less distorted nuclei within such cells. Sudan III and silver-impregnation preparations showed the presence of changed lipoids. In the ganglia of goats that lived three weeks or more there was unmistakable evidence of complete cell destruction, in some instances extending from the point of inoculation well into the ganglion. Lipoid pigmentation was distinctly shown by Sudan III and silver impregnation. Histologically, these changes were parallel to those found in the ganglia in cases of exophthalmic goiter in the human subject.

(*c*) In goats from which the thyroid had been removed in from three days to three weeks after the injection, the cells of the thyroid parenchyma were actively functionating, as was evidenced by their swollen size, granular protoplasm, well-rounded nuclei and the presence of large quantities of feebly staining secretion within the acini. The histological appearance was closely parallel with that found in the thyroid in early cases of exophthalmic goiter. When a period of three months had elapsed between inoculation and removal of the thyroid the thyroid parenchyma showed evidence of exhausted function in that the cells were no longer swollen, their nuclei were more or less crenated and the colloid secretion within the acini was densely staining.

Conclusion. From the above experiments, it would appear that irritation from the presence of certain bacteria within the cervical sympathetic ganglia of the goat may produce histological pictures within the ganglia and in the thyroid which parallel those found in the various stages of progressive and regressive exophthalmic goiter. This evidence supports the suggestion that in exophthalmic goiter the thyroid received its stimulus to overfunction through its nerve supply and as a result usually of a local infection in the cervical sympathetic ganglia.

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DISCUSSION

Dr. Meltzer said that one statement in Dr. Wilson's paper seemed to him quite unusual, namely, that a single stimulation or even a few stimulations of the nerve fibers supposedly going to the thyroid should be sufficient to cause profound atrophic changes in that gland. Dr. Meltzer may not have entirely understood, but the statement reminded him of Dr. Halsted's experience, who published nearly three decades ago a statement that the slightest injury of the thyroid causes a hypertrophy of that gland. So far as I know that statement was generally accepted as correct. Two or three years ago, however, Dr. Halsted himself reported that in a recent series of experiments he convinced himself that the hypertrophic changes brought about in the thyroid were not due to the injury of that organ but to an infection.

Dr. Wilson, closing and in reply to the suggestions, stated it had been well established that the nerve supply of the thyroid comes from the thyroid plexus, and thus from the cervical sympathetic ganglia. Answering a question interposed at this juncture by Dr. Meltzer as to whether Dr. Wilson was aware of the work of Dr. Cannon, Dr. Wilson said yes, and that Cannon's work was corroborative of his; further, that he, the speaker, had gone over Dr. Cannon's sections of cat's thyroids and found in them what he had found in the goat's thyroids, namely, exhaustion of the stimulated parenchyma. He had elsewhere noted his indebtedness to Cannon's work for the suggestion of stimulating the thyroid through the sympathetic nerves. Certain it was that though the evidence was not wholly positive, they were getting a very marked effect upon the secretion of the thyroid gland owing to the impossibility of collecting and measuring the secretion, yet, at the same time, they had secured the changes in the parenchyma of the glands as shown and that these changes could be interpreted only as associated with increased function of the gland.

FURTHER EXPERIENCE IN THE TREATMENT OF TYPHOID FEVER BY THE INTRAVENOUS INJECTION OF SENSITIZED TYPHOID VACCINE SEDIMENT

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A LITTLE over a year ago Chickering and I[1] reported on the treatment of over 50 cases of typhoid fever by the intravenous injection of typhoid vaccine, which results, with some additional cases, were presented before this Association a year ago. Since that time opportunities have been available for the study of two additional groups of cases: the first at the Presbyterian Hospital in New York City, made possible through the great courtesy of Dr. Warfield T. Longcope; and the second a group of 28 cases occurring in the Providence Hospital, Oakland, California, and rendered available for this study by the kindness of Dr. Edward Von Adelung. The latter group of cases is of particular interest not only as being considerable in number, but as giving us our first opportunity of dealing with epidemic typhoid. These 28 cases occurred among a group of workmen employed in constructing the San Pablo dam in Contra Costa county, and were due to a well-traced contamination of drinking-water which led to the occurrence of some 52 cases of typhoid fever, that have been reported on from the epidemiological stand-point by Drs. Geiger and Macmillan.[2]

The method we have employed in treating typhoid has already been detailed, but may be repeated in essentials here. Treatment has consisted in the intravenous injection of the Gay-Claypole sensitized vaccine sediment, a preparation obtained from multiple strains of the typhoid bacillus of local and general origin, so chosen

as to represent the characteristic antigenic groups of the typhoid bacilli that have been tentatively separated by Hooker, whose work has since been confirmed by Weiss. The vaccine is further prepared by treating these strains of typhoid bacilli with a rabbit-immune serum of high agglutinating titer, subsequently washing them, and then killing and precipitating them by means of absolute alcohol. This killed vaccine is then dried to constant weight and ground in a mechanical mortar until the bodies of the bacteria are thoroughly disintegrated. The endotoxic substances are extracted by means of carbolated saline and the supernatant fluid rejected, the sediment of ground bacterial bodies being alone employed for injection. The use of this sensitized vaccine sediment has been reported on elsewhere in reference to its use in prophylactic immunization.[3] It has been found that this vaccine may be injected intravenously in adults in doses beginning with 0.02 of a milligram and gradually increasing in some instances to 0.06 of a milligram, without any harmful effects, although such injections give rise to a characteristic train of symptoms which seem intimately connected with the favorable results obtained. Our experiments herewith reported represent 1200 injections, and it may confidently be stated that no harmful results in the cases of typhoid fever involved, either immediate or delayed, are referable to the vaccine.

A synopsis of the cases of which this is a report is given in Table I, which we may proceed to explain in some detail.

TABLE I

Total cases examined	194
Non-typhoid cases	62
Cases of typhoid on clinical basis alone	8
Cases of proved typhoid	124
Cases of proved typhoid not treated	26
Cases treated as suggested	98

One hundred and ninety-four cases of suspected or possible typhoid were examined by full laboratory methods, and of these, 62 cases, by agglutination tests, blood cultures, and in some instances stool and urine examinations, could not be identified as typhoid fever. All of these 62 cases could eventually be likewise dismissed on clinical evidence as well, as certainly not typhoid. There remain,

however, 8 cases which may have been typhoid fever on the basis of the clinical examination, which, however, it was impossible to confirm by laboratory tests; these cases are not included in our series, although two of them were treated in the manner described with beneficial results. There remain, then, 124 cases of typhoid fever that may be accepted as certain on the basis of both clinical and thorough laboratory examination. Every case of proved typhoid fever, with the twenty-six exceptions to be mentioned presently, was treated in accordance with the method to be fully outlined at a later point.

We should here perhaps explain and possibly defend our decision to treat every available proved case. It has been a frequent custom among clinicians who wish to investigate any new method of therapy to treat a certain number of cases in a given series by the method in question, leaving another group of cases of variable size under the routine previously adopted for the object of furnishing what have been regarded as controls. This procedure has been patterned after the methods ordinarily in vogue in animal experimentation, where truly controlled experiments are essential and convincing. It should be pointed out, we believe, that no group of human cases of typhoid fever or of any other disease can so be utilized except on the basis of a relatively large number of cases, where purely statistical methods of computation may be employed. Chance infection in typhoid fever in no way represents the methods of experimental precision which are possible in animal experimentation, and no two cases of typhoid fever exactly resemble one another. In the first place, the infecting dose when derived from various sources of contagion must be extremely variable, and even in the case of an epidemic, as in the San Pablo epidemic, which forms a part of our series and where the contaminating dose may be assumed to be somewhat similar in all the cases, the widest variation is found in the individual reaction to the infection, a variation based on the individual resistance natural or acquired. We regard, then, the use of alleged control cases in a study of this sort as fallacious, inasmuch as they do not really control at all, and should prefer to judge our results, (1) on the basis of what actually occurs in each and every case following the treatment employed, and (2) by comparison

of this group of cases, although limited, with other recognized standards in respect to mortality incidence, duration of the disease, and the percentage of occurrence of complications. We believe that judgment arrived at on this basis requires more convincing evidence, which we believe is fortunately present in this particular case.

Twenty-six of our cases of proved typhoid were not treated, either because it was impossible to treat them, or because we believed that any results obtained in them might lead to an incorrectly favorable interpretation. Thus in 9 of our cases the temperature had already begun to fall, or the patient was indeed already afebrile. Three of them really represented a post-typhoidal condition—osteomyelitis, for example. Five refused treatment. In 3, intravenous injections could not be given. Concerning 3, no record is obtainable, and in 3 more death occurred before the laboratory diagnosis had been arrived at.

It should be emphasized that in no case was treatment withheld on account of the seriousness of the patient's condition, a fact of significance in consideration of the low mortality obtained. In 2 at least of our 6 fatal cases the prognosis seemed inevitably fatal when treatment was begun.

We may consider for a moment the results of laboratory diagnosis in the 98 cases that were actually treated. The diagnosis was based first on the agglutination test (Widal) in all instances, on blood cultures in 94 of the 98 cases, and in many instances on detection of the typhoid bacillus in the stool and urine. The agglutination tests were made by the macroscopic method with the employment of formalin-killed cultures of the typhoid bacillus. We have stated in our previous communication that complete sedimentation of the added bacteria overnight, even in dilutions as low as one to ten, are, if not absolutely diagnostic of typhoid fever (or typhoid vaccination), at least strongly presumptive evidence of it. We may mention here that of 67 control, non-typhoidal cases tested in connection with this series, the Widal was negative by this method in a dilution of 1 to 10 in 64 instances (95.5 per cent.). The 3 exceptions were liver abscess, bronchitis and trichiniasis, in the first and last of which previous typhoid could by no

means be ruled out. On the basis of the lower dilution 94.8 per cent. of our cases gave a positive Widal at some time during the disease, or if a higher and usual standard of dilution of 1 to 40 alone is acceptable, 91.8 per cent. of our cases were positive. Blood culture (made by adding 10 c.c. of blood to 200 c.c. of 10 per cent. bile broth) were positive in our series in 71 per cent., and in 13 per cent. only were blood cultures negative when more than one examination had been made. In 68 per cent. of the cases both Widal and blood cultures were positive. In 2 cases alone of the 98 were both Widal and blood cultures negative, in which instances diagnosis was based on the isolation of the typhoid bacillus from the stools or urine.

The intravenous injection of our vaccine produces a series of distinct symptoms which vary markedly in intensity with individuals and with the dose employed. The usual amount on initial injection has been $\frac{1}{50}$ mg. (corresponding to 150,000,000 bacteria), and a corresponding dose in children, who, as in prophylactic immunization against typhoid, react less markedly than adults to corresponding amounts. We shall later refer to the findings of other investigators who have used other vaccines intravenously and who have described alarming or even dangerous symptoms following their employment. It should be noted, however, that our vaccine, owing to its sensitization and the removal of endotoxins, certainly gives less perturbing, and, so far as we have observed, no really untoward effect. It seems necessary to produce a moderate reaction in order to effect the desired result, and the dosage in successive inoculations has been increased slightly in order to produce a similar train of symptoms on each inoculation, which a continuance of the same dose usually fails to do. The injection of the vaccine intravenously is followed in from fifteen minutes to an hour by a chill which lasts for a few minutes to ten or fifteen. This chill, or shaking, is not accompanied by a feeling of coldness, but rather by a sense of involuntary, spasmodic, muscular contraction. The chill is accompanied by a rise in temperature of 1° to 3°, which reaches its height within three hours after injection and then falls. There may be a rise of temperature without a chill or the reverse. The rise in temperature is accompanied by a

leukopenia, which may fall as low as 2000 to 3000 to the cubic centimeter. The chill is accompanied by an increase in the pulse rate and may be associated with slight cyanosis, slight respiratory distress, and frequently a sense of discomfort.

The temperature reaches normal or subnormal in about twelve hours. This fall in temperature is accompanied by sweating, which may be profuse and last for several hours, relaxation, and usually general amelioration of such symptoms as headache, delirium and the like. The patient often feels perfectly well, and this condition, even when transitory, seems beneficial. Coincident with the fall in temperature there occurs a rise in the leukocytes, which may reach as high as 40,000 and which are characterized by a relative polymorphonuclear increase. We shall later refer in reviewing the work of others with similar methods to the dangers that have appeared with slightly different vaccine preparations and to the contra-indications to such injections that undoubtedly exist. We may repeat, however, that in our experience of 1200 injections reactions of this sort have never appeared harmful, either immediately or ultimately, and contra-indications seem, in the light of increasing experience, to grow progressively fewer.

No detailed method of procedure can be prescribed for treating any given case of typhoid fever by this method. The best results seem to be obtained by provoking a distinct but not too severe reaction of the type outlined. The dose necessary to produce such a result varies markedly with the individual and the particular balance already established between the typhoid bacillus and the reaction antibodies in the host. The temporary drop of temperature to normal may become permanent and remain there, in which case no further injections are required, except for the prevention of relapse. If the temperature again rises over a period of two or three days, the injection should be repeated in slightly increased amount, and so on until the desired result is produced or further injections are judged futile. A considerable number of injections may be given with perfect safety. As many as fifteen or sixteen have been given in certain instances, but if no striking result is obtained following three or four injections, at two- or three-day intervals, very little effect from the treatment may be expected.

It has seemed wise to us previously to separate our cases into three rather definite groups in respect to the results produced by the

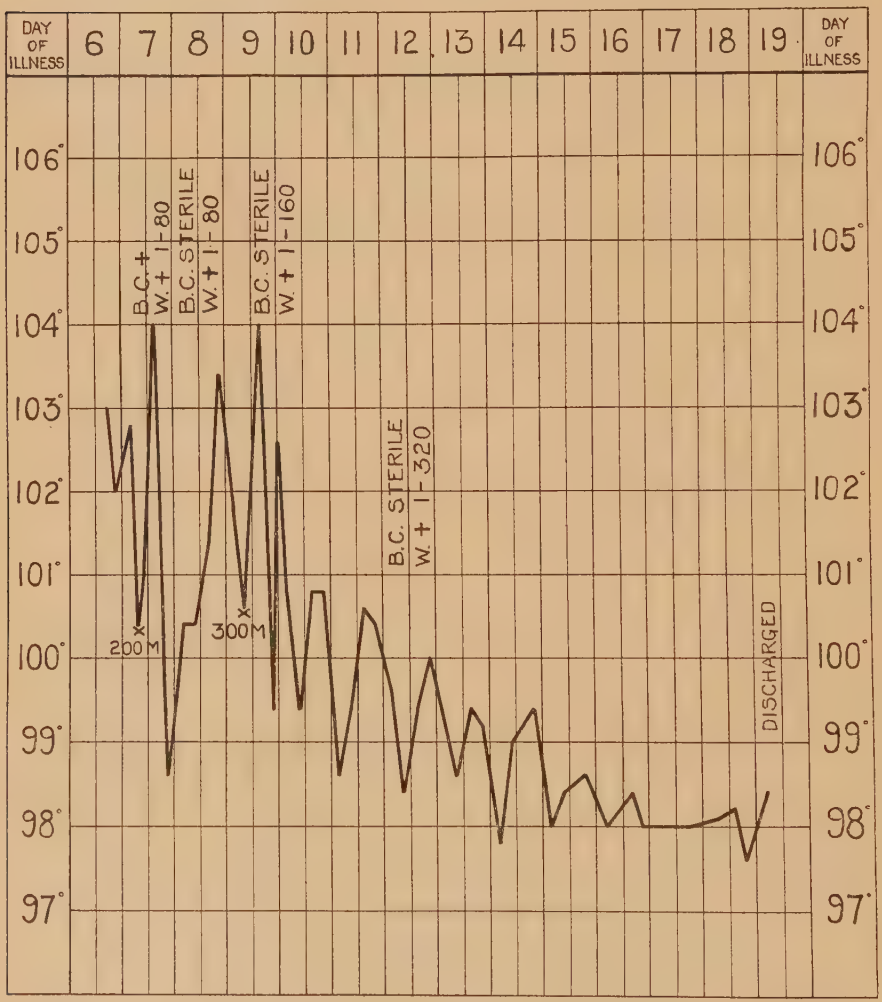

FIG. 1.—Case No. 35. Illustrating an abortive cure.*

* The data in these charts are abbreviated as follows: B. C. = blood culture; W = Widal; A. T. = antityphoid serum; 75 M. = sensitized vaccine corresponding to 75,000,000 typhoid bacilli. The temperatures indicated are the highest maxima forenoon and afternoon on each day per rectum.

vaccine injections, and we see no reason to change this grouping in the light of further experience. We believe that this grouping,

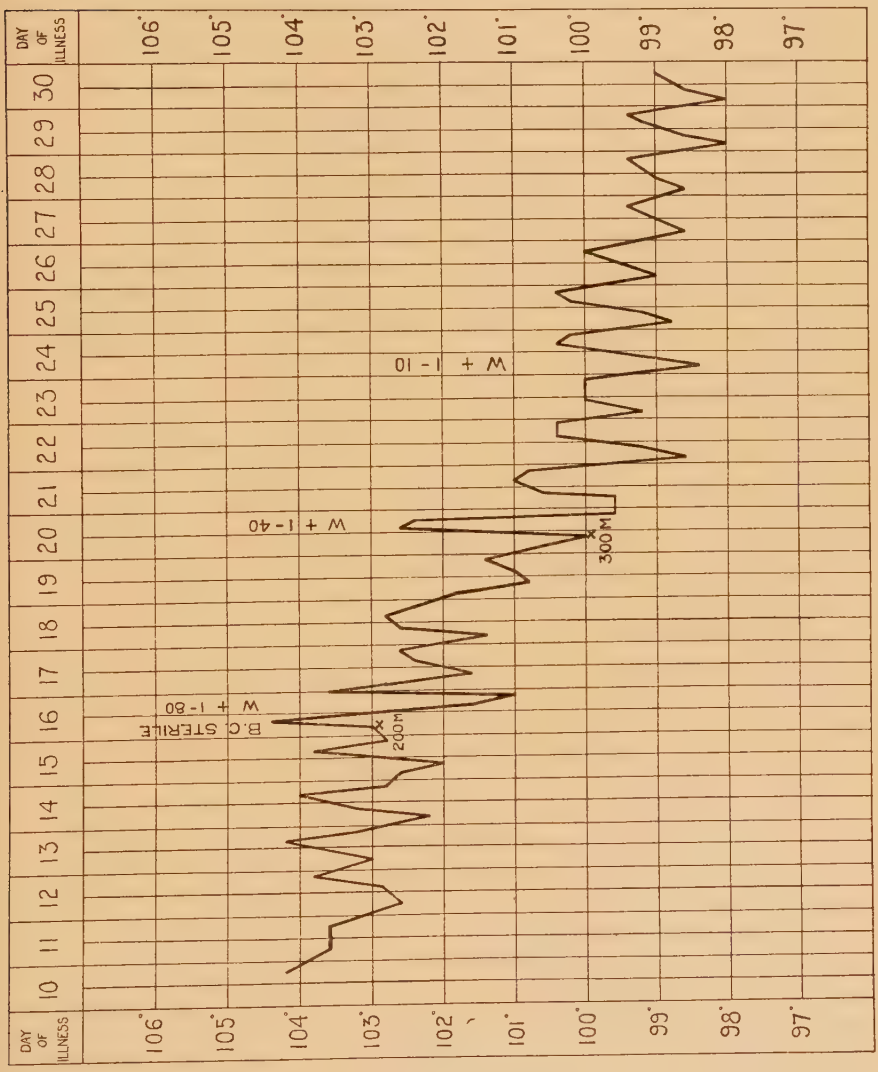

FIG. 2.—Case No. 43. Illustrating a benefited case.

based on results produced, is a conservative one and by no means represents all the benefit that attends this method of treating

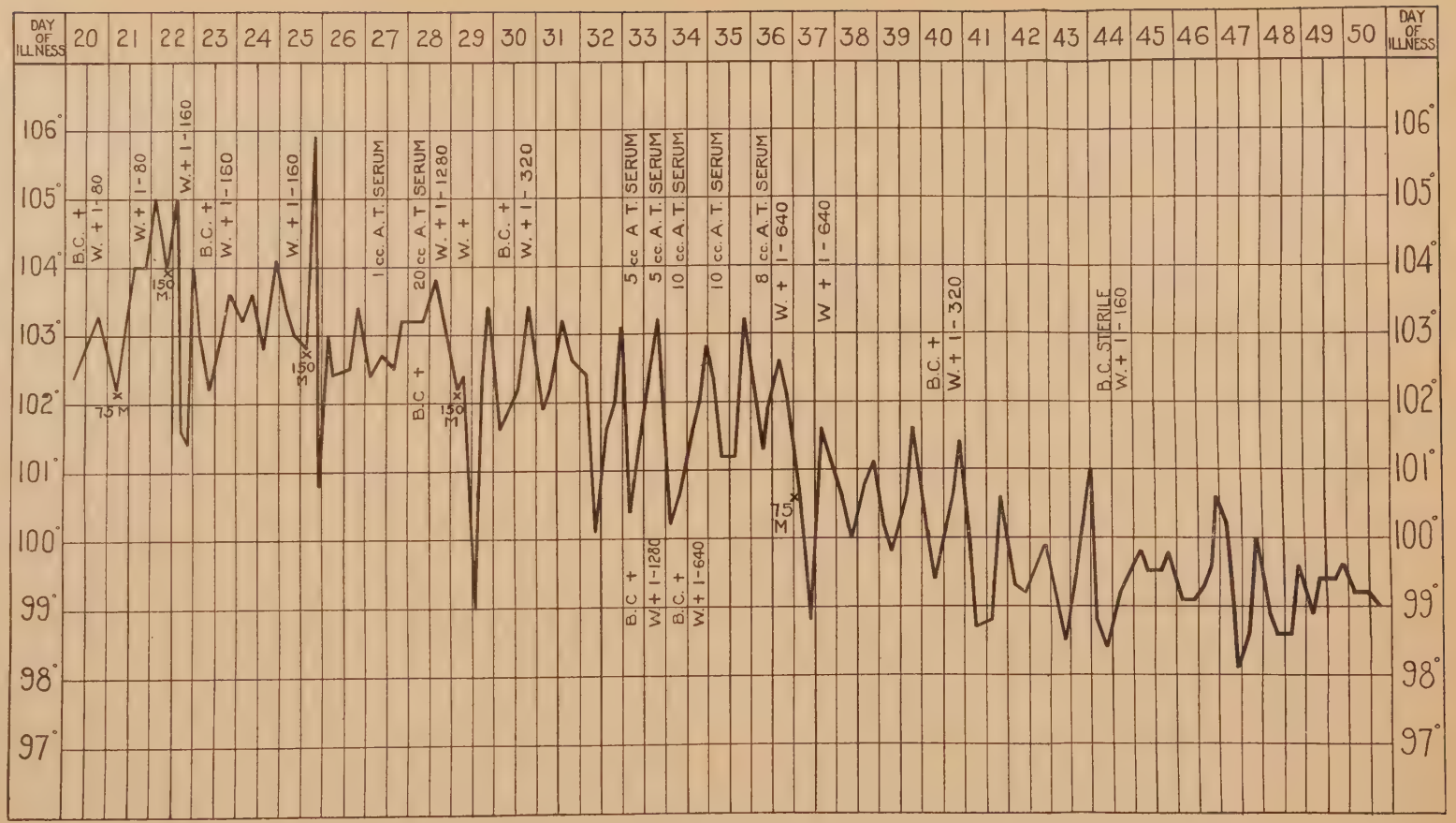

FIG. 3.—Case No. 47. Illustrating an unaffected case.

typhoid fever. We have briefly referred to the fact that the temperature excursion with return to normal is accompanied by subjective feelings of well-being, although at times of slight weakness, and would seem to be both immediately and ultimately of benefit to the patient. Such subjective amelioration is, of course, open to error in interpretation, but would seem not only to us but to others who have watched our cases to be frequent and of a convincing nature. The nurses, for example, in charge of the cases not only volunteer remarks as to the benefit produced by the vaccine injections, but emphasize the lessened care which patients treated in this manner entail. We prefer, however, to base our judgment as to the good results of the method rather on the more objective results that have been produced, the shortening of the duration of the fever, its frequent abrupt termination in an abortive form, the lessening of mortality and of complications in particular. We have classified the three groups of results obtained as abortively recovered, as benefited, or as unaffected, and herewith present again charts from our previous article illustrating types of recovery of these three kinds (Figs. 1, 2 and 3).

A summary of our 98 cases classified under these three headings proves of interest not only in respect to results achieved but as bearing on the mechanism by which it is effected. In Table II are expressed certain characteristic findings in each of these groups of cases under consideration, which we may briefly refer to in drawing certain conclusions as to their significance.

TABLE II.—SUMMARY OF RESULTS IN 98 CASES OF TYPHOID TREATED BY INTRAVENOUS INJECTION OF SENSITIZED VACCINE SEDIMENT

	No.	Age.	Widal titer.	B. C. per cent.	Treatment begun, day.	No. of treatments.	Permanent normal.	Duration of treatment.
Aborted .	33	26.2	296.0	36.6	13.4	1.88	20.4	7·0
Benefited	32	24.2	156.5	70.9	14.8	3.20	30.6	15.8
Unaffected	33	28.8	114.8	84.8	13.7	4.85	46.8	33.1

In the first place it will be seen that our cases may be divided into three almost exactly equal groups in respect to results produced. These groups, moreover, are of almost identical age, and it is also found that treatment was begun on the average at practically the

same time in the three groups. They differ in practically all other respects. We find in the first place that antibody formation, as evidenced by the Widal or agglutinin titer in the cases before injections were begun, varies markedly in accordance with the eventual outcome of the case in question. In the abortively cured cases the Widal is found to be on the average over twice as high as in the unaffected cases, whereas the benefited cases lie intermediate between the two groups. A strong Widal is evidence, then, of a good prognosis, not only in respect to these treated cases but probably also in untreated cases, to judge from the experience of others. Inversely correlative with the strength of the Widal is the occurrence of the percentage of positive blood cultures in the three categories under discussion; whereas the cases that respond less well to treatment are found to give positive blood cultures in nearly 85 per cent. of cases, those that recover abruptly on treatment had positive blood cultures in only 36.6 per cent. The benefited cases again lie intermediate between the two. These relations between blood cultures and antibody formation we have already referred to as representing a balance established in the patient before intervention between the infecting agent and the resisting power of the host. When the resisting power is strongly developed, a favorable outcome may be more confidently expected.

This group of cases which we have classified as abortively cured or abortively recovered suggest in some respects the mild or abortive typhoid cases which are discussed in most extensive monographs on this disease. The typhus levissimus of Griesinger, the typhoidette of Brouardel, or abortive typhoid form a well-recognized group or groups that must occur in every considerable collection of cases of typhoid fever. Estimates vary as to the exact proportion of such cases, as may normally be expected. It is probable, as Curschmann[4] suggests, that at least two groups should be formed—the mild typhoid fevers and the abortive typhoid fevers, the latter more frequently though by no means invariably characterized by a somewhat abrupt rise and fall of temperature and an abbreviated fastigium. McCrae in his 1500 cases found 3 per cent. of mild forms of the disease, and, in addition, 0.1 per cent. of his cases recovered by crisis. Letulle[5] found that these two types of the disease occurred

particularly in certain epidemics and in children. He finds something over 17 per cent. in the cases of the disease which he collected. This figure may certainly be regarded as an extreme maximum of occurrence. According to Curschmann the abortive and mild forms frequently have only three to six days of fever, and almost never over ten or twelve days, with which statement Hare and Beardsley[5] would agree. At all events the cases of mild and abortive typhoid together must constitute a relatively small percentage of all in spite of the figures of Letulle. Hare and Beardsley note that Coleman found only 24 such cases in five years' experience at the Bellevue Hospital in New York. At all events no such number as one-third of all the cases, as in our series, could be found in this way without some type of intervention. It may further be noted that our cases almost invariably have occurred beyond the limit of ten to twelve days set by Curschmann, and have practically invariably been characterized by a critical fall of temperature, and what is more important still, show a direct relation between this critical fall and the injection of vaccine. Our cases do not represent the mild epidemics of Letulle, nor has any considerable number of them been furnished by children. They have been gathered over three seasons and in widely different localities. As may be anticipated the abortively recovered cases represent generally, when estimated before treatment was begun, the milder cases of the disease in this series. Our characterization of a preponderance of these abortively cured cases as milder has no relation, however, to the small group of mild and abortive forms that have just been discussed. We have endeavored to register our impression as to the severity of each case before treatment was begun, and our results are expressed in Table III, where it is found that many more severe cases occur among those that remain unaffected by treatment, and many more mild cases occur among those that are aborted, whereas the benefited cases would seem to lie intermediate between the two.

TABLE III.—GENERAL CONDITION OF CASES BEFORE TREATMENT

	Severe.	Moderate.	Mild.
Unaffected	26	6	1
Benefited	10	17	5
Aborted	4	13	16

It is evident, then, that the milder cases react better to treatment than the more severe, but even the most severe ones will in some instances at least be benefited and even aborted. We believe the effects actually produced are best represented by the figures given under "Permanent Normal Temperature" and "Duration of Treatment" in Table II. It is found that a permanent normal temperature was obtained in the third of the cases that are called aborted on an average at about the twentieth day. When we consider that the treatment of these cases was not begun until the thirteenth day, the really significant figure of seven days as the average duration of treatment required to restore the patient to an essentially normal condition, so far as the temperature is concerned, is obtained. We find, moreover, that it took on the average a little under two injections to produce this result. The fall of temperature by crisis, which is exemplified in the chart (Fig. 1) used to illustrate the abortive cure, is characteristic of this category, although the abrupt fall may not occur in every instance on the first injection.

The benefited cases, again, are well typified in the illustrative chart (Fig. 2); each successive injection of vaccine produces a permanent fall in temperature on the average of 1°, and it may require several, on the average a little over three injections, to reduce the temperature to a permanent normal. The average duration, then, of these cases is found to be 30.6 days, and the duration of treatment the more significant figure, 15.8 days.

The cases that have been listed as unaffected, although showing the ordinary temperature excursions following each injection, are characterized by a prompt return of the temperature to its original or nearly its original height. The impression has remained in the minds of many who have seen these cases that they are really benefited, but since we have taken the reduction of temperature as our criterion of results, we prefer not to emphasize any good effect that may have occurred in these cases, beyond the diminution in complications and mortality, to which we shall presently refer. Even in this group of cases the average duration is by no means extraordinary (46.8 days), although it does exceed somewhat perhaps a normal average duration of cases of typhoid fever. It is

extremely difficult to estimate what such an average duration usually is. Curschmann regards the mild cases as lasting on an average of twenty-one to thirty-three days. In McCrae's[7] figures the average febrile was thirty-one days. It should be noted that our figures refer to the total duration of the disease from its initial symptoms, so far as they can be estimated from the patient's history, and not from the known duration of the fever itself. The group of cases, then, that were best affected may reasonably be regarded as having run a distinctly short course, and the average of all cases, which is about twenty-nine days, is not markedly different from McCrae's thirty-one days.

The mortality in this series of 98 treated cases is 6.6 per cent., which, when we consider that the cases were treated over a period of three seasons under varying conditions of care in private houses as well as hospitals, and, moreover, treated in different parts of the country, is certainly a very satisfactory figure. The average mortality is usually figured at 10 per cent. The cases of death were predominantly due to the accidents of typhoid, 3 to hemorrhage, complicated with perforation in two instances, 2 to a combination of laryngitis and bronchopneumonia, and 1 only to typhoid toxemia.

The complications, again, were few in number, and only 13 in all in the entire 98 cases (13.2 per cent.). This means not that 13 cases showed complications, for there were indeed only 8 cases which showed complications, but the total number of complications was 13. These complications were as follows: pyelitis 1 case, lobar pneumonia 1 case, laryngitis 2 cases, bronchopneumonia 2 cases, toxemia 1 case, hemorrhage 4 cases, perforation 2 cases. The percentage of hemorrhage (4 per cent. +) and of perforation (2 per cent.) is certainly below what may be expected as the usual average for these complications; 5 to 10 per cent. for hemorrhage and 3 to 4 per cent. for perforation. Although the earlier study of vaccine therapy in typhoid certainly led to the impression, particularly when the vaccine was administered subcutaneously, that complications were diminished (Krumbhaar and Richardson,[8] Callison[9]), more recent work would seem to show that no distinct effect on the complications can be expected by the more recent intravenous

type of treatment (Szecsy,[10] Wiltshire,[11] Reiter,[12] and Guinon and Malarte[13]).

The relapses are of particular interest in this series of cases because they show what we believe to be the effect of a method of treatment which we suggested in our previous article, and which has since been emphasized by others. It seemed from our previous work that relapses would be less likely to occur if the intravenous injections were followed, when the temperature had returned to normal, by a set of three subcutaneous injections on alternate days of the regular prophylactic dose (800,000,000 bacteria or 0.1 mg. of our sensitized vaccine).* This method of treatment has likewise been recommended by Meyer,[14] Meyer and Altstaedt,[15] and Wiltshire.[11] There were 10 relapses (10.2 per cent.) in our series, which may be compared with the usual average of 11.4 per cent. given by McCrae. Eight of our relapses, however, occurred in cases in which the intravenous injections were not followed up by the subcutaneous treatment, so that when we come to divide the cases in relation to this treatment into two categories we find that relapses occurred in only 5.39 per cent. of the subcutaneously treated cases (37) and in 11.59 per cent. of the cases in which intravenous injection alone was given (69). We believe, then, that this method should be followed in every case.

Summary of Recent Literature on Vaccine Therapy of Typhoid. We may next consider the very considerable number of articles which have dealt with different methods of vaccine treatment of typhoid fever in the past few years. We do not intend at this point to repeat an historical account of the development of vaccine therapy in this disease, but wish here to give a summary of the results in very recent years, roughly from 1913 to 1917, both as indicating the extent to which these investigations have been pursued, and more particularly as indicating which of these methods is best. We have summarized in Table IV the results obtained by a considerable series of observers who have used different, or in some cases several, methods of vaccine treatment.

* These vaccine injections in the convalescent typhoid will in a few instances cause a rise in temperature of a degree on the same or the following day.

TABLE IV.*—SUMMARY OF RESULTS OBTAINED BY RECENT OBSERVERS (1913–17) IN THE TREATMENT OF TYPHOID FEVER BY VACCINES ADMINISTERED IN VARIOUS WAYS

	Observers.	Total cases.	Estimates based on.	Benefited, per cent.	Mortality, per cent.
Untreated vaccine subcutaneously	30	1001	512	46	14.5
Sensitized vaccine subcutaneously	14	593	239	69	8.0
Untreated vaccine intravenously	22	501	233	62	13.0
Sensitized vaccine intravenously	12	487	316	85	11.0

It will be noted, first, that the most frequent method of vaccine treatment in typhoid has been the subcutaneous injection of ordinary and usually heat-killed, untreated typhoid vaccines. The thirty authors on whose work we base our estimates, it should be repeated, are only very recent writers on the subject and by no means indicate the extent to which this method has been employed in previous years, a summary of which may be found in some of the articles quoted. This method of treatment, however, still remains somewhat the predominating one. Later modifications that have been introduced are, first, the use of sensitized vaccine subcutaneously, and then the injection intravenously either of plain vaccine or of sensitized vaccine. We have endeavored to estimate the results obtained by each of these methods of treatment. It is obvious that any such estimate is with difficulty arrived at. In the first place, many authors give wholly indefinite accounts of

* The authors referred to in this summary are herewith given, a division being made in respect to the type of vaccine employed and its method of administration, as in the table. (1) Recent authors reporting on the use of untreated vaccine subcutaneously: 1911, Fletcher; 1912, Sadler, Callison; 1913, Fornet; 1914, Josue and Belloir, Weil, Sacquépée and Chevrel, Guinon and Malarte, Pensuti, Daretti; 1915, Goldscheider and Aust, Bourke, Evans and Rowland, Feistmantel, Mertz, Peiper, Krumbhaar and Richardson, Gröer, Wiltshire and MacGillycuddy, Löwy, Lucksch and Wilhelm, Kahn, Reiter, Meyer, F., Brach and Fröhlich, Boselli; 1916, Lemanske, Peutz, Whittington, Zupnik, Müller and Leiner, Waitzfelder. (2) Authors who have employed sensitized vaccine subcutaneously: 1912, Ardin-Delteil, Negre and Raynaud; 1913, Ardin-Delteil, Negre and Raynaud, Roques, Boinet; 1915, Petrovitch, Ardin-Delteil, Negre and Raynaud, Garbat, Feistmantel, Szecsy, Liebermann, Fellner, Löwy, Lucksch and Wilhelm, Boral, Deutsch; 1916, Galambos, Mayer. (3) Authors who have injected untreated vaccine intravenously; 1913, Thiroloix and Bardon; 1914, Kraus and Mazza, Kraus; 1915, Biedl, Ditthorn and Schultz, Csernel and Marton, Reibmayr, H., Mazza, McWilliams, H. I., Holler, Paulicek, Meyer, Rhein, Leutz, Ortiz, Acuna and Belloc; 1916, Faginoli, A., Petzetakis, Zupnik, Müller and Leiner, Löwy, Lucksch and Wilhelm. (4) Authors who have injected sensitized vaccine intravenously: 1912, Ichikawa; 1914, Meyer and Altstaedt; 1915, Biedl, Eggerth, Holler, Sladek and Kotlowski, Koramyi, Landsberger, Löwy, Lucksch and Wilhelm; 1916, Rohoni, Galambos; 1917, Coronia.

even the number of cases that they have treated, and even when the number is mentioned, the results obtained are frequently referred to as good, bad or indifferent. The figures in the third column, on which the estimates of the percentage of benefit derived from each method of treatment is based, represent all the cases in the total number considered, in which a definite statement of result by the author was made.

One thing stands out preëminently in a consideration of this total recent literature, and that is that the great majority of the authors believe the vaccine treatment, irrespective of the method pursued, to be of benefit. The very few individuals who remain unconvinced of the value of the treatment or mention dangers in its employment have based their opinion on very few cases and a corresponding inexperience in the use of vaccine (Zupnik,[16] Peutz,[17] Sladek and Kotlowski,[18] Deutsch[19]). It seems further distinctly indicated from this table that the degree of benefit, and to some extent the reduction of mortality, would seem to increase with each successive innovation that has been suggested in recent years. The best results unquestionably seem to have been obtained by the intravenous injection of sensitized typhoid vaccine, the sensitization having been either by the use of convalescent serum, as advocated by Ichikawa, or by the use of a vaccine similar to the Besredka living typhoid vaccine. The superior results of sensitized vaccines and of intravenous injection over other methods is further evidenced when we consider those authors who have used more than one of the methods outlined. Thus, we find that Löwy, Lucksch and Wilhelm[20] obtained better results in their cases by giving plain vaccine intravenously than when it was given subcutaneously. Similar conclusons were drawn by Ortiz, Acuna and Belloc.[21] Paltauf,[22] Holler,[23] and Feistmantel[24] all conclude that sensitized vaccines produce better results than unsensitized vaccines.

It remains now to offer what explanation we may as to the mechanism by which the unquestionably beneficial effects of vaccine therapy in typhoid are brought about, and, particularly, why the intravenous treatment is better and the sensitized vaccine superior to the unsensitized. These relative differences seem to emerge inevitably from the attentive consideration of the literature that we

have given, and have, at least in part, been preceded or followed by theoretical explanations of heuristic value.

Specificity of Vaccine Therapy. We were careful to state in our previous article that the method of therapy which we were advocating could by no means be regarded as strictly specific in view of the results that had been obtained by other investigators. These results have since been markedly extended and may now be more readily classified than a year ago. In the first place it has been found that beneficial effects of a very similar nature and characterized by similar reactions to those described have been produced in typhoid fever by the administration of vaccines prepared from bacteria other than the Bacillus typhosus. Kraus[25] was the first to note that he obtained beneficial results on the intravenous injection of colon as well as of typhoid vaccines. Ludke[26] and Lucksch[27] both obtained results with colon vaccine, and the latter author obtained a favorable effect by gonococcus vaccines and by sodium nucleinate. Zupnik[16] has utilized a vaccine made from the mouse typhoid bacillus as less toxic and as useful as true typhoid vaccine. Reibmayr,[28] who has employed colon and cholera vaccines in typhoid as well as typhoid vaccine, concludes that the former, although beneficial, are not so good as that derived from the specific microorganism.

In a similar manner it has been found that other acute infectious diseases may be beneficially affected by the intravenous injection of their corresponding vaccines or of other vaccines. Thus Kraus[29] notes the beneficial effect produced in cases of puerperal sepsis and pyocaneous infections by the use of a colon vaccine. Rhein[30] notes the beneficial effect in paratyphoid fever of typhoid vaccine. Nolf[31] utilized peptone solutions advantageously in streptococcus infections. Miller and Lusk[32] have employed typhoid vaccine by intravenous injection advantageously in acute, subacute and chronic arthritis.

This leads to a consideration of the less complex proteins and, indeed, simple inorganic salts that have been employed with claim to equally favorable results both in typhoid and in other acute infections. Ludke[26] has described the use of deutero-albumose in typhoid, Weichardt[33] the employment of albumin solutions, and

Nolf, as already mentioned, has used 0.5 gram of peptone dissolved in 200 c.c. of normal saline and administered intravenously. Baradulin[34] has utilized dextrose solutions in considerable amount in cases of surgical sepsis, and Weichardt and Engländer[35] have obtained similar results with normal physiological saline alone. The use of colloidal gold (Colibiase) by Letulle and Mage,[36] Barachon,[37] Gay,[38] Labbé and Moussaud,[39] and Delbet[40] would seem simply another instance of the non-specificity of the reaction that we have described.

It should be reiterated that in each and all of these instances the beneficial effects produced, which are undoubted, are brought about by the intravenous injections of a non-specific vaccine, a less complex protein, or even a complex or simple organic or inorganic substance. These injections, moreover, have all been characterized by the train of symptoms we have described with typhoid vaccines, of chill, temperature excursion, and the results in the nature of critical recovery have been similar, though probably differing in relative percentage.

Mechanism of Cure in Intravenous Vaccine Therapy. This proof of the non-specificity of the most favorable results that can be produced by a typhoid vaccine in typhoid fever should not only not discourage us but lead us to inquire further into the mechanism of the reaction on which this benefit depends. In our previous work (Gay and Claypole, Gay and Chickering) we have been led to attribute significance to two factors which we believe not only concerned, but of importance, in the reaction which is produced by intravenous vaccine injections. The first of these factors is the hyperleukocytosis which following our observations has also been found to occur by a number of authors (MacWilliams,[41] Holler,[23] Löwy, Lucksch and Wilhelm,[20] Lucksch,[27] and Rohonyi[42]). It has also been shown that many of the substances which in a non-specific manner may lead to the same effects as, for example, nucleon (Melnikowa and Wersilowa[43]), and colloidal gold (Busquet,[44] Barachon[34]), also increase the leukocyte count, to which fact their results have been attributed.

As a second factor on which the degree of benefit obtained would seem to depend is the antibody content of the patient. This we

have already brought out in previous work and repeated in this article, where it is found that the strength of the Widal titer seems to vary directly with the benefit that results from injection. This observation, moreover, would agree with the incidental observation of a number of observers that prognosis in general is more or less dependent on the strength of antibodies in the patient, and, particularly, that the prognosis of vaccine injection likewise bears some relation to the degree to which the individual has reacted against the infection. Of like significance is the extremely mild and favorable course of typhoid fever in the vaccinated. Koranyi[45] has found that the opsonic index rises after vaccine injection in typhoid, and Inez Smith in our laboratory has apparently been able to demonstrate a distinct relation in the degree to which the opsonic index increases after intravenous injection and the result produced. In other words, the opsonic index rose much more markedly in the cases that were abortively cured than in either the benefited or the unaffected cases. We have frequently found that the agglutinin titer rises after the vaccine injection.

Our previous hypothesis as to the mechanism by which cure was effected in the most striking instances was, briefly, that it was due to a coöperation between the leukocytes that were called out by the injection and the antibodies already present in the patient, which latter substances acting as tropins caused the digestion and destruction of the typhoid bacilli in the body by the increased white blood corpuscles. We gave several reasons for regarding this mechanism as probably apart from the now proved relation of the antibody strength and the leukocytic increase to the result obtained. In the first place, it can be shown by blood culture in some, though by no means all, instances that the bacteria disappear rapidly from the peripheral circulation following the injection. Similar results have been obtained by other investigators. This working hypothesis may or may not be the correct or ultimate explanation of the results produced by this non-specific reaction in typhoid fever and in other acute infections. There are other explanations which are probably no more ultimate and which, indeed, are not of necessity in any direct conflict with the one we have presented. Jobling and Petersen[46] have attributed the results

produced by the reaction as due to a disturbance of ferment, antiferment balance, the antiferment being absorbed and the ferment being allowed to act. This explanation is certainly a very attractive one. Teague and McWilliams[47] in recent experiments on rabbits also bring forth certain results which must be taken into consideration in explaining this type of therapy. They find that the injection of vaccine in rabbits produces a refractory condition which renders these animals temporarily more resistant to infection with the typhoid bacillus. They would attribute the results produced in the favorable cases of treatment to an overflowing of bactericidal substances, which are found to be present in the circulating blood, into the remoter lymph spaces which serve as metastatic foci in typhoid fever, and the consequent destruction of the bacteria that are present in them.

It makes very little difference whether we regard the leukocytes or bactericidal ferments in the serum as the cause of the ultimate destruction of the bacteria, with which recovery seems to be associated. It is probable, indeed, that the white blood cells are the sources of the ferments, and we see no reason why these various factors and experiments that have been brought out by Teague and McWilliams, Jobling and Petersen and ourselves will not eventually stand in harmony in the ultimate explanation which may soon come.

In our previous article we expressed the hope that it might be possible to increase the percentage of most favorably reacting cases by supplying the hypothetical lack of antibodies, which seems to be characteristic of the unaffected cases. We mentioned two or three cases in which we apparently were able to produce abortive cures, although the antibody content was low, by injecting an immune serum followed by vaccine. We have since continued these experiments, but it must be confessed with no very encouraging result. In the first place, it seemed necessary to determine the best type of protective or curative antiserum that could be produced. We have utilized goats for the purpose and immunized individual animals on the one hand with sensitized, and on the other with unsensitized living typhoid polyvalent vaccines. It was found possible to compare the protective value of such sera with consider-

able accuracy by injecting them subcutaneously in mice with a subsequent intraperitoneal injection of typhoid bacilli grown on blood media. No striking differences in the protective value of the unsensitized as against the sensitized sera was evident. We then tried the effect of such sera in a few human cases of typhoid and found that the serum alone usually produced the same type of non-specific reaction brought about by the vaccine. A great deal of work has recently been done in France on the use of antityphoid serum of this general type, particularly the serum advocated by Rodet. In a series of articles from 1910 to the present time Rodet and his collaborators[48] have described the preparation of an antityphoid serum in horses and the results produced by it. Similarly favorable results have also been obtained by Remond and Manvielle[49] and Étienne.[50] A survey of their results, however, does not lead one to believe that the results with the serum even when given intravenously are as good as those produced by means of vaccine, and, indeed, the results produced would seem due rather to the reaction which the injection causes, and which differs only in degree from the reaction produced by vaccine, than to any antibodies that are present in the serum. Abortive cures are reported by these observers: Étienne, for example, in 12 cases out of 200 and Rodet in a somewhat larger percentage, but these abortive cures would seem to be less frequent than when vaccine is employed, and the shortening of the disease, although distinct, is by no means as pronounced as by the use of vaccine.

In view of the non-specificity of the characteristic reaction on which the vaccine treatment of typhoid depends it may be questioned why we continue to advocate typhoid vaccine in preference to any of the other substances that have been employed. To repeat our opinion of a year ago, we would say that typhoid vaccine alone can build up the specific immunity to the typhoid bacillus, on which, at least in part, the cure may depend, and with which a lessening of complications would seem certainly to be associated. Typhoid vaccine, moreover, when employed in the form of the Gay-Claypole sensitized sediment is a harmless substance, convenient to employ and active in very small amounts. Again, the degree of leukocytosis on which the result obtained would seem in

part to depend is, we still believe, increased in a relatively specific manner when a sensitized vaccine is used. We are aware that McWilliams[51] has been unable to repeat some of our experiments on specific hyperleukocytosis. We are not prepared to state to what her failures were due. The conditions of her experiments are by no means fully stated. The leukocyte counts were begun at periods which perhaps were after the maximum degree of leukocytosis, and in all events our crucial experiments, depending on the injection of sensitized vaccines in normal animals, were not attempted. One positive set of experiments is sometimes more valid than many failures to repeat them; failures which are due not to inaccuracy but to our unavoidable misunderstanding of all the conditions which have been influential in producing the original results.

Summary and Conclusions. This article records our experience in the treatment of 98 authenticated cases of typhoid fever over a period of two and one-half years by the intravenous injection of a polyvalent sensitized typhoid vaccine sediment (Gay-Claypole vaccine). The cases were observed for the most part in hospitals, but to some extent in private houses. The series includes cases studied in New York City as well as in California. We regard the treatment as indicated in any case of typhoid fever that is still febrile, on the basis of our results which seem excellent. The mortality in these cases was low (6.6 per cent.) and the complications few. Relapses were distinctly reduced in those cases in which the intravenous injections were followed by a series of three subcutaneous inoculations after the temperature had reached normal.

Our estimate of the beneficial results which have followed this treatment, apart from the probable reduction of mortality and complications, is based on the following facts:

1. In one-third of the cases the temperature fell critically following the first or second injection, and a permanent normal was established on the average within a week after beginning treatment.

2. In a second series of cases each injection was followed by a permanent decrease of a degree or more in the temperature.

3. Subjective benefit, apart from temperature changes, seemed to follow the majority of inoculations.

The treatment is perfectly harmless with the particular vaccine and under the conditions employed.

A detailed consideration of similar methods of therapy that have been studied with increasing interest in the last two years would seem to show that intravenous injections are far superior to subcutaneous injections of vaccine, and that sensitized vaccines are better than plain typhoid vaccines. It appears that the reaction is not strictly specific in that a similar type of reaction, chill, temperature excursion, etc., which is characteristic of the intravenous vaccine injections, may be produced by similar administration of other vaccines, of other proteins, and, indeed, of salt solution. There is some evidence, however, that relatively better results are produced by the use of the typhoid vaccine which in addition aids in establishing an active immunity against the specific microörganism concerned. The exact mechanism by which the benefit or cure is effected is as yet uncertain, but it is at least marked by a temporary increase in the number of leukocytes and is probably dependent on the strength of antibodies already present in the individual patient. Our efforts to supply these antibodies by means of an antityphoid serum have not met with great success, and the beneficial effects that others have obtained with antityphoid serum would seem to be due to a mechanism similar to that following vaccine injections, but less effective than the latter.

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ELECTROCARDIOGRAPHIC OBSERVATIONS IN TOXIC GOITRE

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The importance of cardiac signs and symptoms in exophthalmic goitre has been a matter of common knowledge since the earliest description of this disease by Parry[1] in 1786. Tachycardia, palpitation, forcible heart action, and less often cardiac arrhythmia are such important factors in the syndrome that Mobius[2] was led to the dictum that "Basedow patients suffer and die through their hearts." It is only within the past decade or so, however, that the cardiac symptoms have been generally considered as due to thyreotoxic influences, rather than wholly or in part due to embarrassment of the right heart following an often hypothetical pressure on the trachea by the enlarged thyroid gland. As this condition constitutes a relatively simple example of an endogenous intoxication, it has seemed advisable to study the changes produced in the electrocardiogram by the intoxication of this disease, with the additional hope that further light might be thrown both on the resulting cardiac condition and on the changes produced in it by surgical operations on the thyroid.

Method. To this end electrocardiograms were taken on 51 goitre patients seeking surgical relief, in as many cases as possible both before and at short and long periods after operation. Information was sought not only as to the rate and rhythm of the heart action in both simple and toxic goitre cases, but also as to the relative size of the chambers of the heart and to other changes in the form of the ventricular complexes of the electrocardiogram

both before and after operation. Endeavor was also made to correlate these findings with the changes observed in the clinical condition of the various subjects examined. On account of the nervous state of many of the patients, fine vibrations of the string were often unavoidable, and occasionally were sufficient to prevent accurate measurement of the *P-R* interval, but did not otherwise interfere with interpretation of records. A still greater handicap was imposed by ineradicable extraneous electrical disturbances which, together with the limitations of the Edelmann galvanometer, prevented the proper complete standardization of records. For this reason it has been impossible to base any deductions on the actual changes in the size of the ventricular complexes observed in a given case after thyroid removal, and only the relative shapes of the various complexes in the pre- and postoperative records could be considered. Time intervals, the diagnosis of existing arrhythmias, and the detection of right or left ventricular preponderance were, of course, not interfered with. Most of the cases here reported were from the clinic of Dr. C. H. Frazier, whom I take this opportunity to thank for placing them at my disposal.

Results. *Clinical.* The clinical data on the cases studied are included in the table on pages 370 and 371.

The usual preponderance of females, the relative youth of most of the cases, and the presence of the characteristic symptoms of the disease are all apparent. It is also obvious that almost all cases were of the toxic, hyperthyroid, or exophthalmic goitre type, and that this diagnosis was confirmed by pathological examination. Thirty-five of the patients submitted to partial thyroidectomy, 10 to artery ligation, and 2 to enucleation of adenomata. Of the ligation group 1 was greatly improved, 5 moderately so, 3 showed little or no improvement, and 1 died. In general this group did not tend to show as marked improvement as did those who had a partial excision. Although 3 of the latter failed to show any improvement after operation it must also be remembered that many of the partial excision group had previously had arteries ligated, without sufficient improvement to obviate further surgical intervention.

TABLE I.—CLINICAL DATA IN TOXIC GOITRE

No.	Name.	Sex.	Age.	Clinical diagnosis.	Blood-pressure.		Symptoms.								Operation.	Pathological diagnosis.	Result.
					Systolic.	Diastolic.	Duration of disease.	Cardiac outline.	Palpation.	Dyspnœa.	Tachycardiac.	Nervous.	Exophthalmic.	Goitre.			
1	B. A.	M	28	Toxic	135	60	3 yrs.	+(Left)	0	0	0	+	+	+	Double ligation	Exophthalmic	Slightly improved.
2	D. A.	F	29	Toxic	110	74	6 yrs.	± (Left)	±	0	0	±	+	+	Single lobectomy	Exophthalmic	Much improved.
3	B. A.	F	24	Toxic	112	53	8 mos.	Normal	0	+	±	±	+	±	One and a half lobectomy	Exophthalmic	Improved.
4	E. B.	F	58	Non-toxic	164	82	14 yrs.	+(Left)	+	0	0	0	0	+	Enucleation	Adenoma	Slightly improved.
5	K. B.	F	13	Non-toxic	....	....	1½ yrs.	± (Left)	0	0	0	0	±	+	Partial excision	Colloid exophthalmic	Improved.
6	R. B.	F	26	Toxic	130	70	1 yr.	Normal	+	..	+	+	0	+	Lobectomy	Colloid	Not improved.
7	C. C.	F	52	Toxic	128	80	15 yrs.	Normal	+	+	+	0	+	+	Ligation	.....	Improved.
8	A. C.	F	21	Toxic	....	....	6 mos.	± (Left)	+	0	0	+	±	+	No operation	.....	Slightly improved.
9	R. C.	F	18	Early toxic	120	85	3 yrs.	Normal	0	+	0	+	0	+	Partial excision	Colloid exophthalmic	Improved.
10	J. C.	M	18	Toxic	115	80	4 yrs.	Normal	+	±	0	+	0	+	Partial excision	Colloid exophthalmic	Much improved.
11	B. C.	F	24	Toxic	125	65	2 mos.	Normal	0	0	+	+	+	+	Ligation	Colloid exophthalmic	Improved.
12	C. C.	F	43	Toxic													
13	M. C.	F	34	Non-toxic	120 145	85 70	4 mos.	+(Left)	+	+	0	+	0	+	Ligation	Exophthalmic	Died.
14	M. D.	F	35	Non-toxic	112	60	15 yrs.	Normal	+	0	0	0	+	+	Enucleation	Colloid adenoma	Slightly improved.
15	A. E.	F	54	Toxic	160	92	1 yr.	+	+	+	0	+	0	+	Double lobectomy	Colloid exophthalmic	Improved.
16	S. F.	F	26	Toxic	135	100	1½ yrs.	Normal	+	±	±	+	0	+	Double lobectomy	.....	Much improved.
17	A. F.	F	24	Toxic	168	68	3 yrs.	+(Left)	±	±	0	+	+	+	Double ligation	.....	Improved.
18	A. F.	F	19	Toxic	120	72	1½ yrs.	Normal	0	0	0	±	0	+	Double lobectomy	Colloid exophthalmic beginning	Improved.
19	A. F.	F	26	Non-toxic	145	105	2½ yrs.	Normal	±	±	0	0	0	+	Partial excision	Colloid cystic	Slightly improved.
20	A. G.	M	48	Toxic	138	72	1 yr.	Normal	+	+	0	±	0	±	Lobectomy	Colloid	Improved.
21	A. G.	F	35	Toxic	148	72	2½ yrs.	+(Left)	+	+	+	±	±	+	Double ligation	.....	Slightly improved.
22	F. H.	F	38	Toxic	....	....	1 yr.	+(Left)	±	+	±	+	0	+	Double lobectomy	Colloid	Died.
23	K. H.	F	17	Non-toxic	120	75	3 yrs.	+(Left)	0	±	0	±	0	+	Partial excision	Colloid	Improved.
24	H. H.	M	32	Toxic	145 135	85 75	10 yrs.	+(Right & left)	+	±	+	+	±	±	Two ligations Two partial excisions.	Exophthalmic	Improved.

25	E. K.	F	19	Toxic	100	65	10 yrs.	Normal	+	0	+	0	Sl.	0	Single lobectomy	Colloid	Improved.
26	A. K.	M	38	Toxic	....	....	Several years	+(Right & left)	+	0	+	0	0	0	Single lobectomy	.....	Not improved.
27	S. L.	F	18	Toxic	145	85	11 yrs.	+(Right & left)	+	0	0	0	0	+	Single lobectomy	Exophthalmic	Slightly improved.
28	M. L.	F	19	Exophthamic	140	....	3 mos.	Normal	0	+	+	0	+	+	Single lobectomy	Exophthalmic	Much improved.
29	I. M.	F	25	Toxic	117	40	4 yrs.	+(Left)	+	+	+	+	+	+	Double lobectomy	Exophthalmic	Improved.
30	M. M.	F	18	Non-toxic	125	70	1½ yrs.	Normal	0	+	0	0	0	0	Single lobectomy	Colloid	Improved.
31	M. M.	F	43	Toxic	129	70	1½ yrs.	Normal	+	0	+	+	+	+	Single lobectomy	Colloid	Improved.
32	J. M.	F	37	Toxic	118	80	3 yrs.	+(Left)	+	+	+	+	Sl.	0	Partial excision	Colloid cystic degeneration	Slightly improved.
33	N. M.	F	17	Toxic	142	70	2 yrs.	+(Left)	+	+	0	+	0	+	Single lobectomy	Colloid adenoma	Much improved.
34	A. M.	F	26	Toxic	148	68	4 mos.	+(Left)	+	+	0	+	+	+	Double ligation Single lobectomy	Exophthalmic	Improved.
35	M. D.	F	11	Toxic	114	48	2 yrs.	+(Left)	+	+	0	+	0	+	Single lobectomy	Adenoma exophthalmic	Much improved.
36	I. O.	F	37	Early toxic	....	....	1 yr.	+(Right)	+	0	+	+	+	+	Single lobectomy Double lobectomy	Colloid exophthalmic changes	Improved.
37	I. P.	F	19	Toxic	115	82	6 mos.	Normal	+	0	+	+	0	+	Double lobectomy	Colloid exophthalmic	Slightly improved.
38	M. P.	F	16	Toxic	135	70	1½ yrs.	+(Right & left)	0	+	+	+	0	+	Double ligation	Hyperplastic lymphadenitis	Improved.
39	M. P.	F	25	Early toxic	117	72	3 yrs.	Normal	+	+	0	+	0	+	Double lobectomy	Colloid	Improved.
40	F. R.	M	39	Toxic	152	70	2 yrs.	+(Right & left)	+	+	+	0	0	+	Single ligation	.....	Died.
41	R. R.	M	29	Non-toxic	100	60	8 yrs.	+(Right)	0	+	0	0	0	+	Double lobectomy	Colloid exophthalmic	Improved.
42	B. R.	F	28	Toxic	130	65	6 yrs.	+(Right & left)	0	+	+	+	+	0	Single lobectomy	Adenoma exophthalmic	Improved.
43	S. S.	F	32	Toxic	133	56	1½ yrs.	(+Right) & left)	+	0	0	+	0	+	Double ligation	.....	Improved.
44	A. S.	F	37	Toxic	103	75	12 yrs.	Normal	+	+	+	+	0	+	Partial ligation	Adenoma	Much improved.
45	G. W.	M	35	Toxic	132 140	75 80	11 yrs.	+(Left)	+	+	+	+	+	+	No operation		
46	A. W.	F	33	Toxic	152 170 165	85 65 50	3 yrs.	+(Left)	+	+	0	+	+	+	Ligation	Exophthalmic	
47	G. D.	M	26	Toxic	133	60	1½ yrs.	+(Right)	+	0	0	+	+	+	Partial excision	Colloid	
48	M. N.	F	33	Non-toxic	....	....	14 yrs.	Normal	0	0	0	+	0	+	Partial excision	Colloid adenoma	
49	B. B.	F	50	Toxic	119	62	3 yrs.	Normal	+	0	+	+	0	0	Partial excision	Exophthalmic	Not improved.
50	R. F.	F	51	Toxic	170	105	2 yrs.	+(Left)	+	+	+	+	0	0	No operation		
51	L. N.	F	43	Toxic and mitral stenosis	95 110	60 55	2 yrs.	+(Right & left)	−	+	+	+	+	+	No operation	.....	Improved.

Of the 47 cases, 7 were greatly improved by the operation, 23 were moderately improved, 14 only slightly or not at all improved,

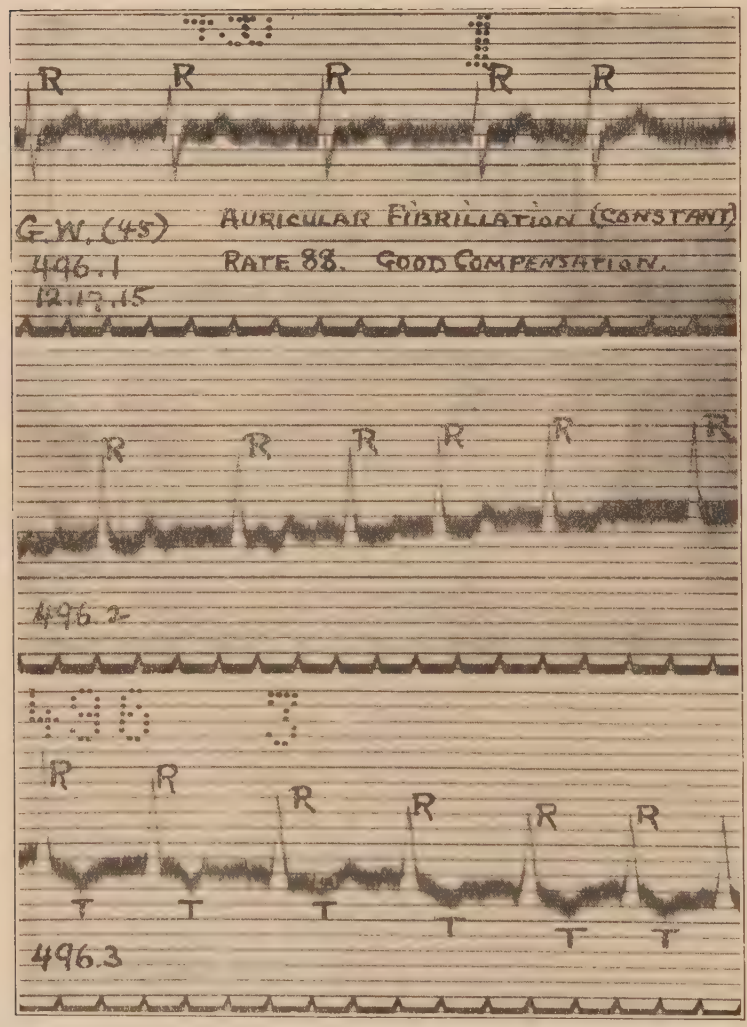

FIG. 1.—Case 45. Electrocardiogram of G. W., showing permanent auricular fibrillation. This and subsequent electrocardiograms were made with the Edelmann galvanometer. As the string could not be standardized with the patient in circuit, 1400 ohms were added as an arbitrary equivalent of the patient's resistance. Platinum strings were used with a resistance varying between 3500 and 5000 ohms. Time intervals are expressed at the bottom of each lead by $\frac{1}{5}$-second intervals. In this figure note (1) absence of sign of auricular contraction (P wave); (2) ventricular arrhythmia (irregular occurrence of R); (3) occasional fine waves of fibrillation.

and 3 died. One of the deaths (Case No. 22) occurred two days after double lobectomy of a colloid goitre and was due to pneu-

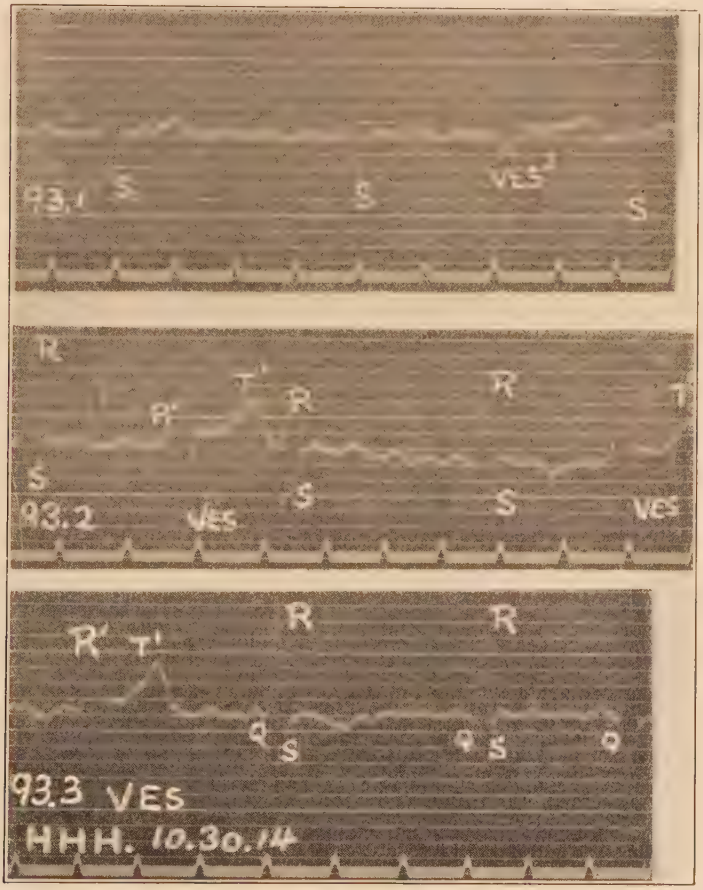

FIG. 2.—Case 24. Electrocardiogram of H. H. H., showing right ventricular preponderance, auricular fibrillation of probably ten years' duration, with occasional ventricular premature contractions arising from several sites. Note (1) that the *S* wave has replaced the *R* wave in Lead I and that the *R* wave of Lead III (R_3) is greater than the *R* wave of Lead II (R_2). Note also that (2) in each lead one or two complexes vary greatly from the normal supraventricular type, and that (3) the same disturbance of mechanism exists as in Fig. 1.

monia complicated by increased thyrotoxicosis; another (Case No. 40) was due to cardiac failure twenty-four hours after ligation of a single artery. It is unfortunately true that in neither case

were adequate premonitory signs evident either in the clinical examination or the electrocardiograms taken a few days before

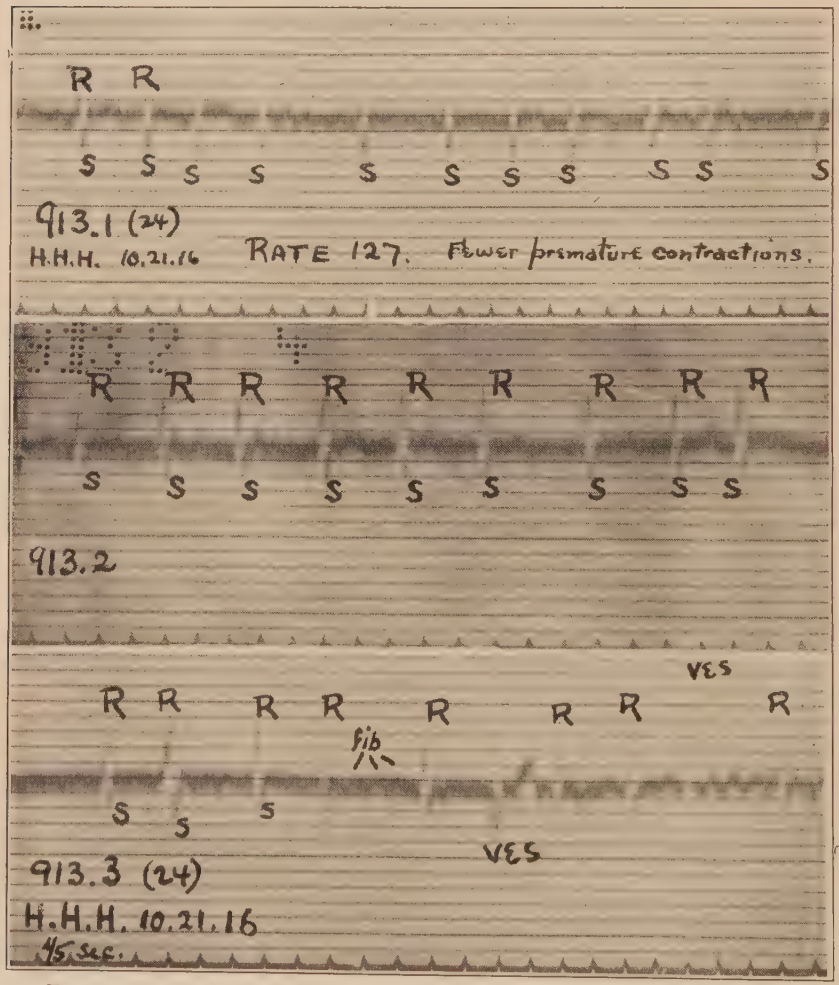

FIG. 3.—Electrocardiogram of same patient as Fig. 2, taken two years later, showing the same picture, except that the premature contractions occur much less frequently.

operation. The third case (Case No. 13), which had failed to improve after ligation of the superior thyroid artery, developed negative *T* waves, which were still present at the time of the second

operation four months later. Her death from cardiac failure two days after the partial excision undertaken at this time tends to confirm the view that negative *T* waves, when not due to digitalis medication, have an unfavorable influence on prognosis. The electrocardiogram of the patient who died from pneumonia showed abnormal *T* waves in Leads II and III, but similar abnormalities were found in 4 other cases (Cases 2, 3, 5, 35) that were improved by operation.

Rhythm. Changes in cardiac rhythm were observed in 11 cases, as follows: sinus arrhythmia, 4 cases; ventricular extrasystoles, 3 cases; auricular fibrillation, 3 cases; auricular flutter, 1 case. The *P–R* interval was prolonged beyond normal limits in 2 cases. As no other adequate cause for such derangement of cardiac mechanism was given in the past history of all but 2 of these cases, it is fair to assume that the majority, if not all, were caused by the thyreotoxicosis, acting not only by its direct toxic effect, but also indirectly through the cardiac hypertrophy and later degeneration thus caused. The fact that most of the cases studied received energetic treatment relatively early in the disease will probably account for the comparative infrequency of the more important arrhythmias and of other gross cardiac changes in this series. This in its turn emphasizes the value of early and thorough medical treatment, followed by prompt surgical intervention in those cases not responding properly to medical care.

The small number of arrhythmic cases affords but little opportunity to judge of the effects of operation on the arrhythmia. The case of flutter and two of the cases of fibrillation were undoubtedly permanent, having been followed over several years without change. Although many different attempts were made at different times to change the auricular flutter into fibrillation or normal rhythm all efforts proved unavailing. One of the cases of auricular fibrillation (Case 51) proved to belong to that interesting group of transient fibrillation, to which attention has elsewhere been called.[3] In Fahrenkamp's[4] series of cases of hyperthyroidism in which transient fibrillation was present the arrhythmia occurred in distinct paroxysms of short duration. In the present case, however, fibrillation was present when the patient was first seen eighteen

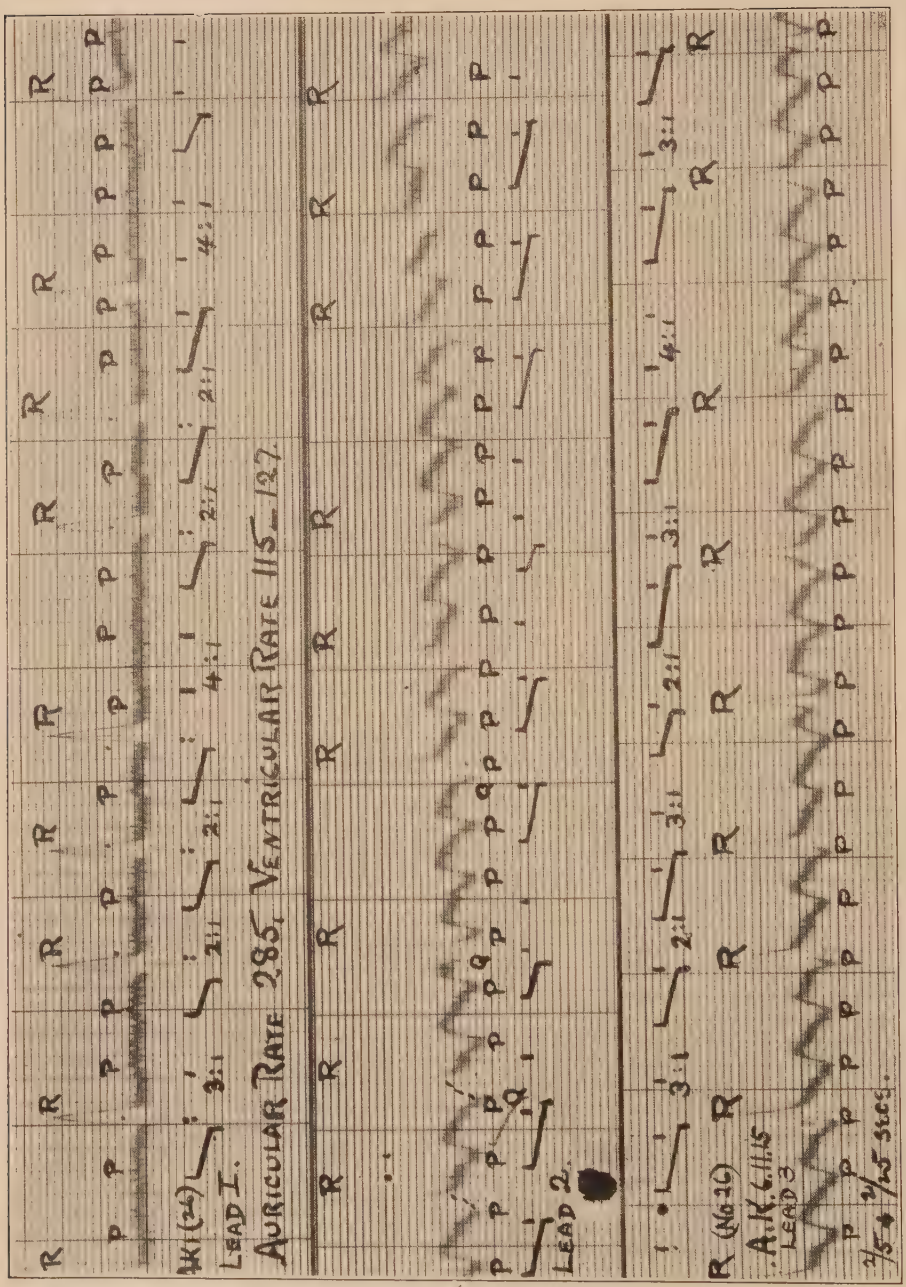
Auricular Rate 285, Ventricular Rate 115–127
Lead I.
Lead 2.
A.K. 6.11.15
Lead 3
1/5 = 1/25 sec.

FIG. 4

months ago. On account of a coexisting mitral stenosis and the absence of data as to the time of origin of the arrhythmia it was thought at that time that an ordinary case of fibrillation with chronic mitral endocarditis was being complicated by hyperthyroidism. The fibrillation persisted apparently as a constant condition until about one month ago, when it was noted that coincident with general improvement the pulse had become regular. Electrocardiograms taken then, and at various periods since then, show that normal rhythm has now supervened. As this occurred coincident with improvement in the hyperthyroidism it is fair to assume that the thyroid and not the endocarditis was the chief factor in the production of the fibrillation.

Of the 3 cases exhibiting extrasystoles only 1 accepted surgical treatment, and in this case the extrasystoles disappeared after operation, just as frequently happens in this type of arrhythmia, when the source of toxemia is removed or diminished.

Although sinus arrhythmia is not usually considered to have any clinical importance it was found to be lessened after operation, along with the signs of clinical improvement. Attention might here be called to the work of Thorne,[5] who considers that, like the other arrhythmias, though in a lesser degree, sinus arrhythmia is never found in a truly normal heart. Whether this belief is accepted or not, any procedure that tends to lessen an existing sinus arrhythmia should be considered a step in the direction of improving the cardiac condition.

Two cases (Cases 4 and 8) showing distinct prolongation of the *P–R* interval in the absence of digitalis medication are the only examples of defective conductivity in this series. Reilingh,[6] however, has shown that more advanced degrees, even complete heart-block, may occur in exophthalmic goitre.

EXPLANATION OF FIG. 4

FIG. 4.—Case 26. Electrocardiogram of A. K., showing auricular flutter, with a varying degree of *A. V.* block, probably of four years' duration. In this as in the other electrocardiograms of this series records were taken from the three customary leads; the tension of the string was so standardized that 1 millivolt caused a deflection of 1 cm. Time intervals in this record are expressed by heavy and light vertical lines across each lead, representing $\frac{2}{5}$ and $\frac{2}{25}$ second respectively (Cambridge galvanometer). Each deflection is lettered according to Einthoven's scheme, and a diagram is added for each lead to illustrate the changing heart block. Note the prominent inverted (diphasic) *P* waves in Leads II and III.

Blood-pressure. The systolic and diastolic blood-pressure was estimated soon after admission to the hospital, and in many cases shortly before discharge. The most noticeable abnormality was

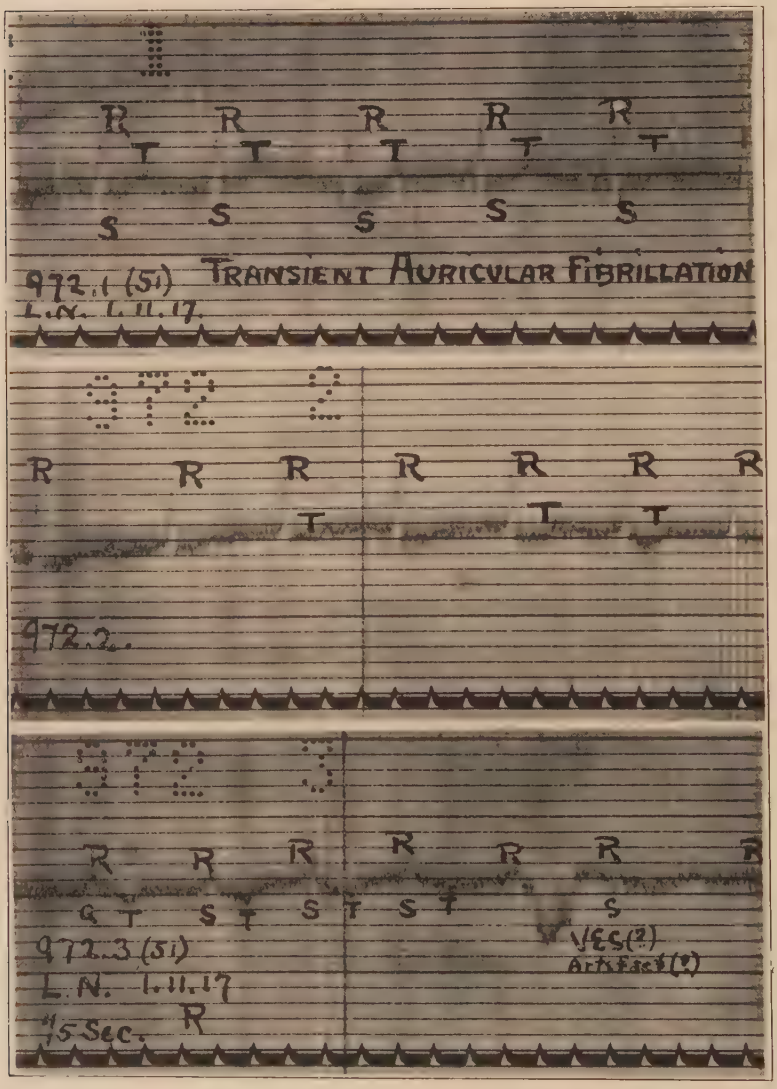

FIG. 5.—Case 51. Electrocardiograms of L. N., showing transient auricular fibrillation. Note that although the ventricular arrhythmia is slight, the same disturbance of mechanism exists as in Fig. 6.

the increased pulse pressure, which was over 60 mm. Hg. in 11 patients who showed no signs of hypertension. The increase in pressure, which was due both to elevation of the systolic and

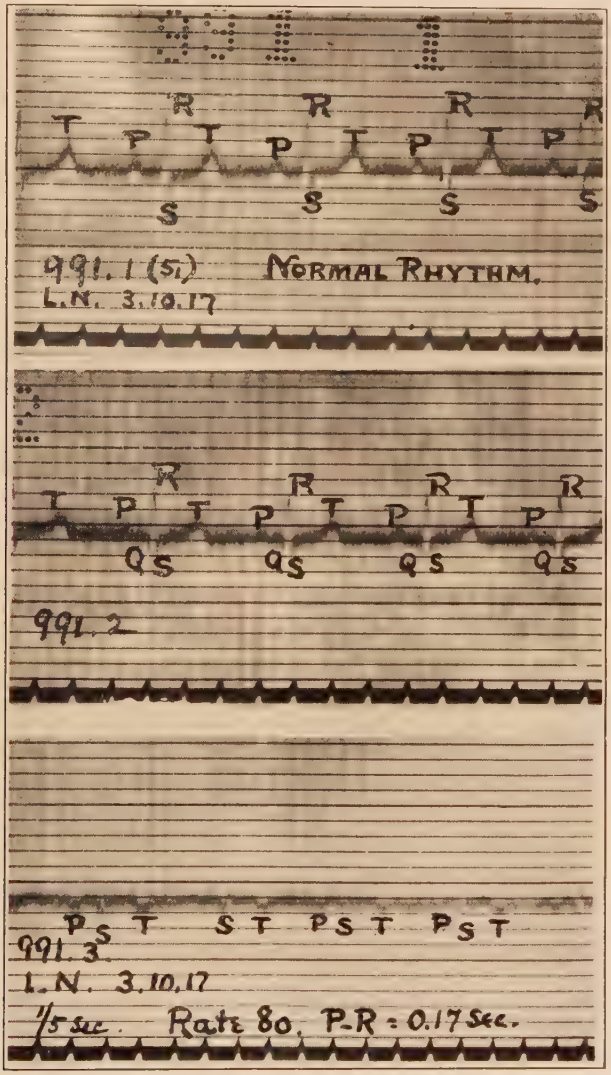

FIG. 6.—Electrocardiogram taken two months later, showing normal rhythm. Note (1) reappearance of *P;* (2) regular ventricular rhythm; (3) absence of irregular waves of fibrillation.

depression of the diastolic pressure, is in all probability to be explained as the vascular response to the overacting heart. In 5

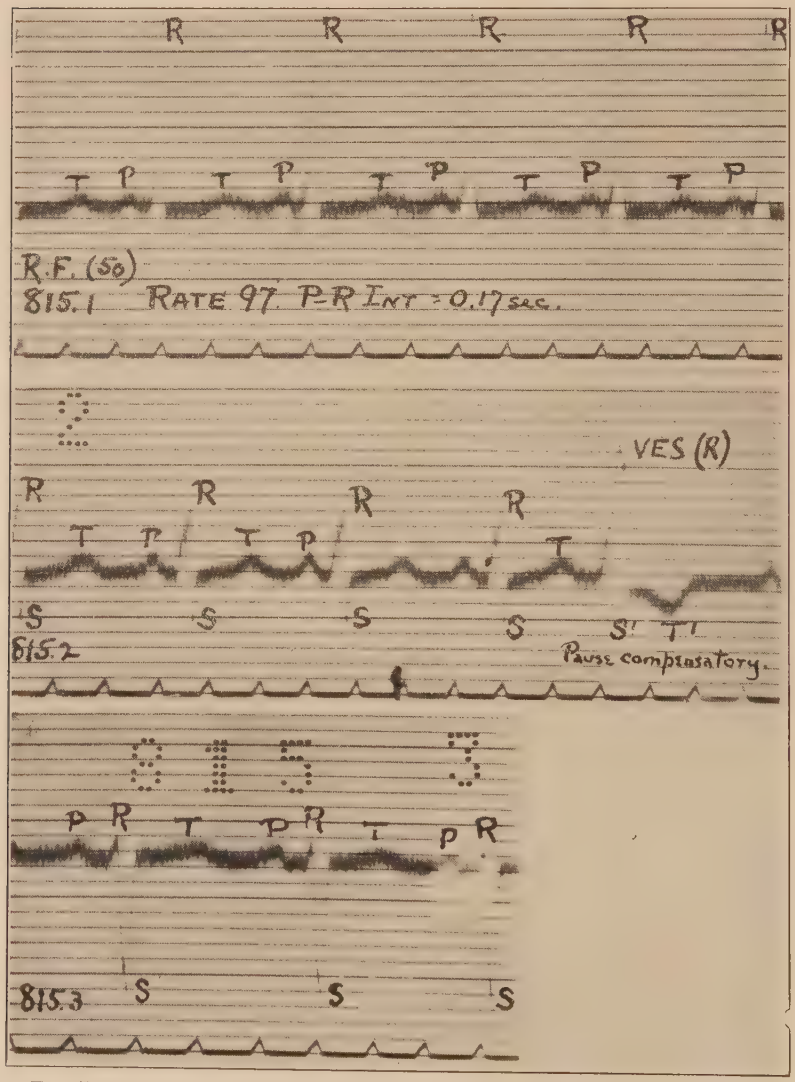

FIG. 7.—Case 50. Electrocardiogram of R. F., showing left ventricular preponderance and one ventricular premature contraction. Note that R_1 is greater than R_2 and that S_3 is greater than R_3. In Lead II note that the last ventricular complex varies greatly from the other complexes of the lead and occurs prematurely (extrasystole).

cases the systolic pressure was above normal limits, but in only 1 were signs of hypertensive nephritis or arteriosclerosis present. In

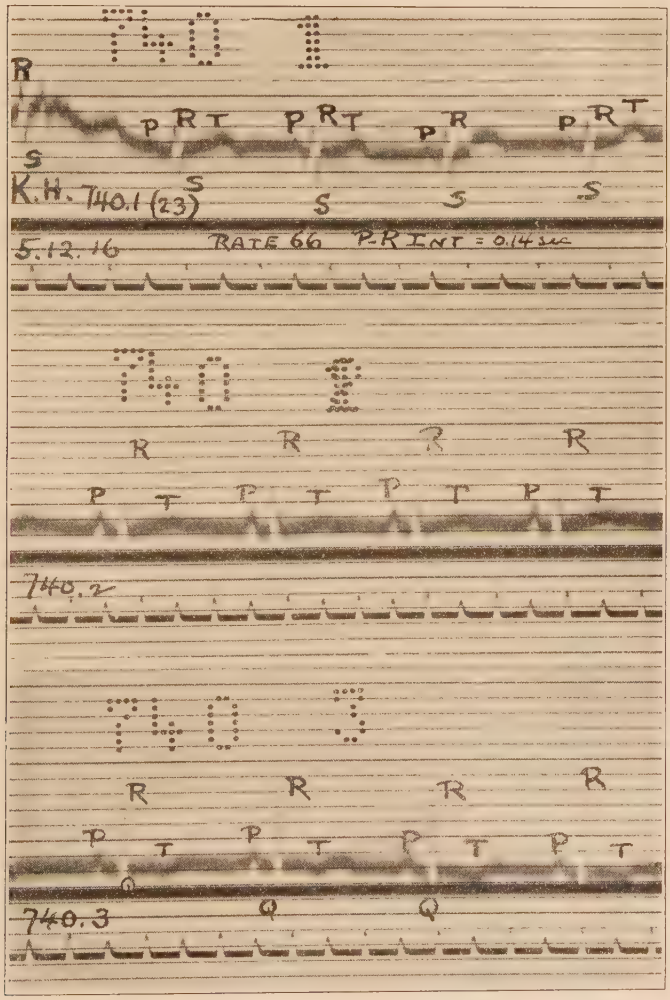

FIG. 8.—Case 23. Electrocardiograms of K. H., showing lessened degree of right ventricular preponderance after operation. Note that whereas S_1 is greater than R_1 in the first record, it is distinctly less in the second. Also R_3, instead of being the same size as R_2, is less than R_2 in the second record.

at least 1 case the pressure fell to normal as the patient improved, so that this too should be considered a sign of cardiac intoxication.

The 3 cases that showed a lowered systolic pressure (below 110) are difficult to explain, but it should be noted in all of these that a normal pulse pressure was preserved. Although due to a different

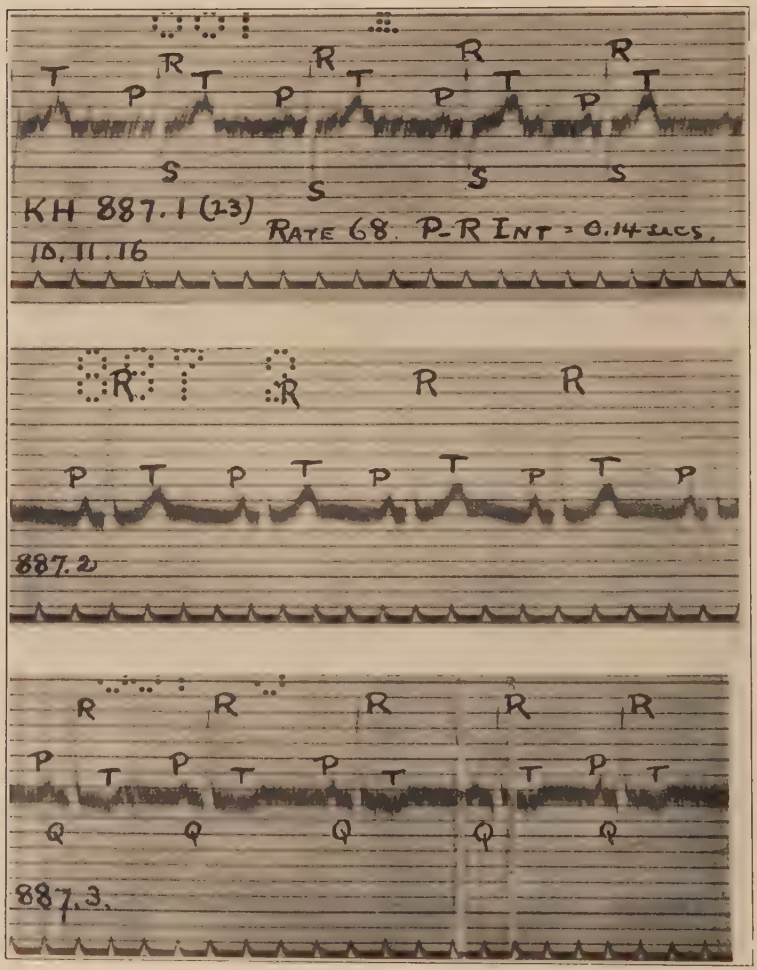

FIG. 9.—Same case as Fig. 8.

kind of disturbance these changes, as has been pointed out by Taussig,[7] are of the same kind as those found in aortic regurgitation, and may be considered as characteristic of toxic goitre.

Changes in Form of the Ventricular Complex. From the point of view of the cardiographer, one of the items of this study that was approached with the liveliest anticipation was the question as to

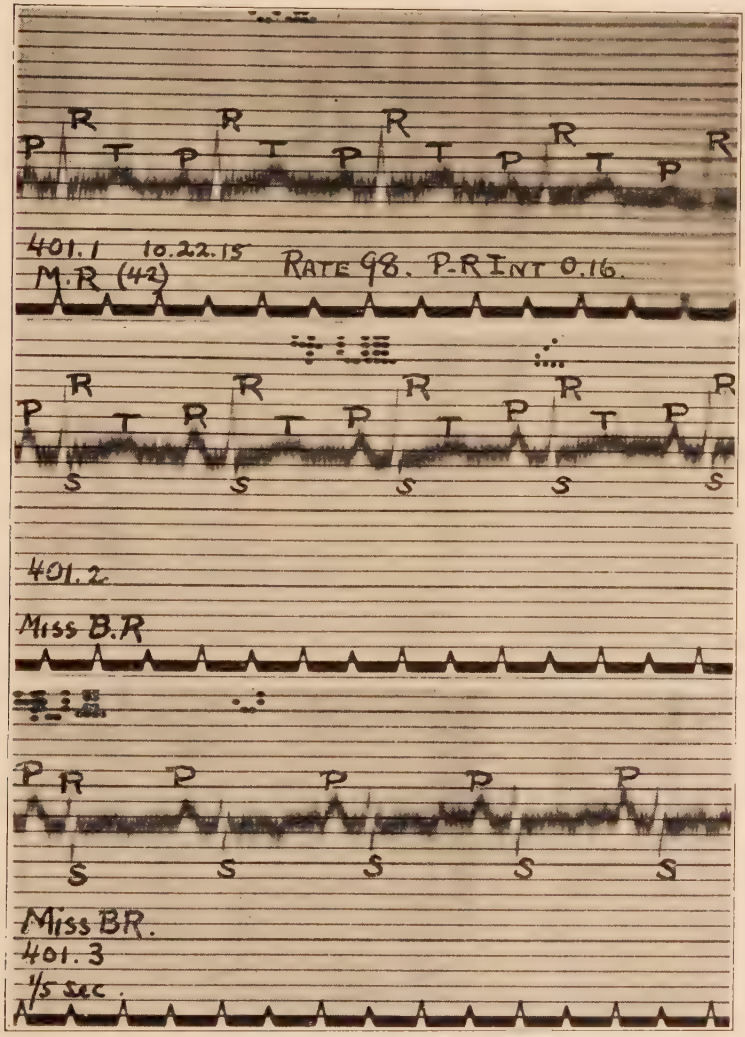

FIG. 10.—Case 42. Electrocardiograms of M. R. before and after operation, showing lessened T wave after operation and a more marked degree of left ventricular preponderance. In the second record note that the T waves are less than in the first (especially in Lead I); also that R_1 has become slightly longer than R_2 and that S_3 is proportionately longer than R_3. (See Fig. 11.)

what effect the thyreotoxicosis and also its treatment by surgical operation would have upon the cardiac function as expressed by

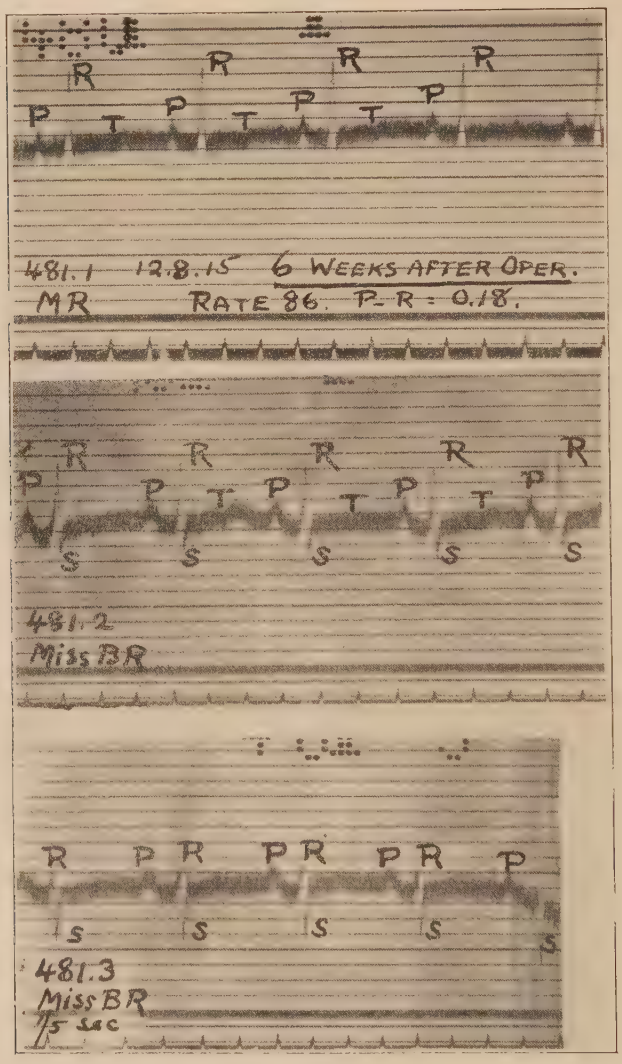

Fig. 11.—Same case as Fig. 10.

the form of the ventricular complex. As an analyzer of cardiac arrhythmias the string galvanometer has already been thoroughly

and satisfactorily exploited. As a gauge of the functional capacity of the heart, however, in demonstrating abnormalities in form of

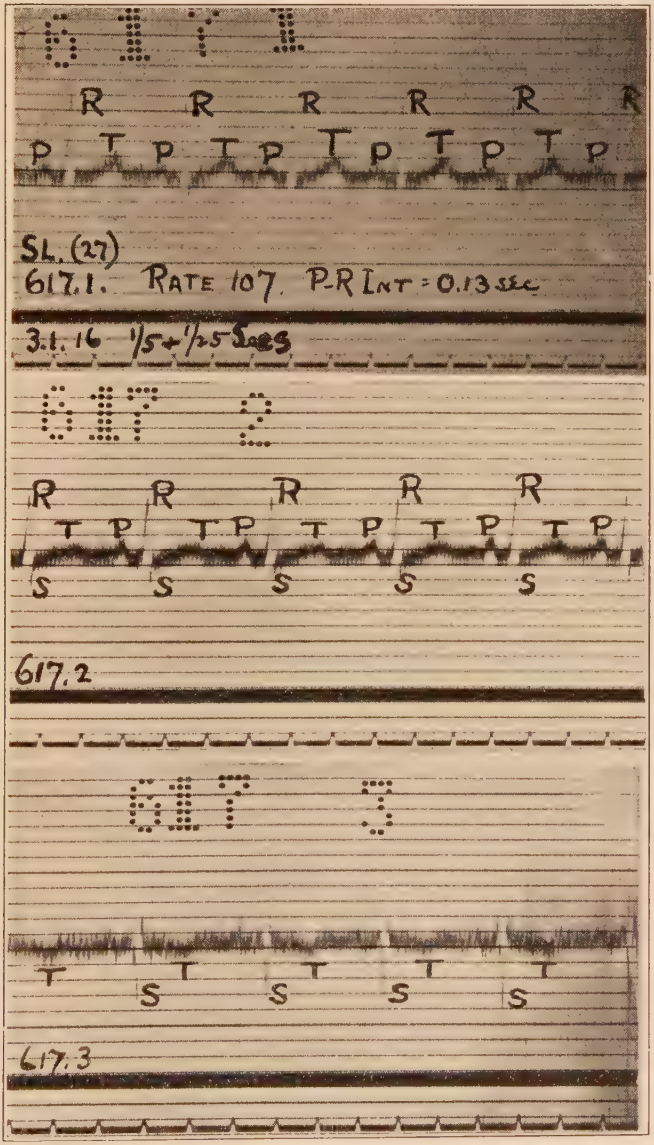

FIG. 12.—Case 27. Electrocardiograms of S. L., showing lessened *T* wave after operation. Time intervals in this record are expressed in $\frac{1}{5}$ and $\frac{1}{25}$ second, by vertical lines, as well as the Jaquet time marker. (See Fig. 13.)

the ventricular complex, its possibilities are still far from being realized. Lewis[9] has called attention to the fact that "if in any subject electrocardiograms which show considerable divergence

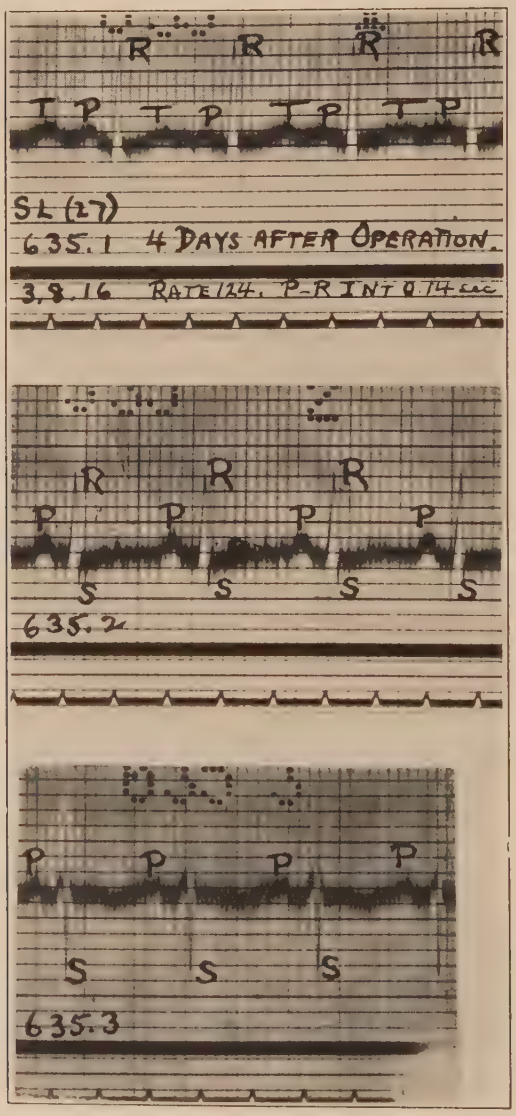

FIG. 13.—Same case as Fig. 12.

from what is regarded as normal are obtained it is probable that the heart is abnormal." This has corresponded to our experience

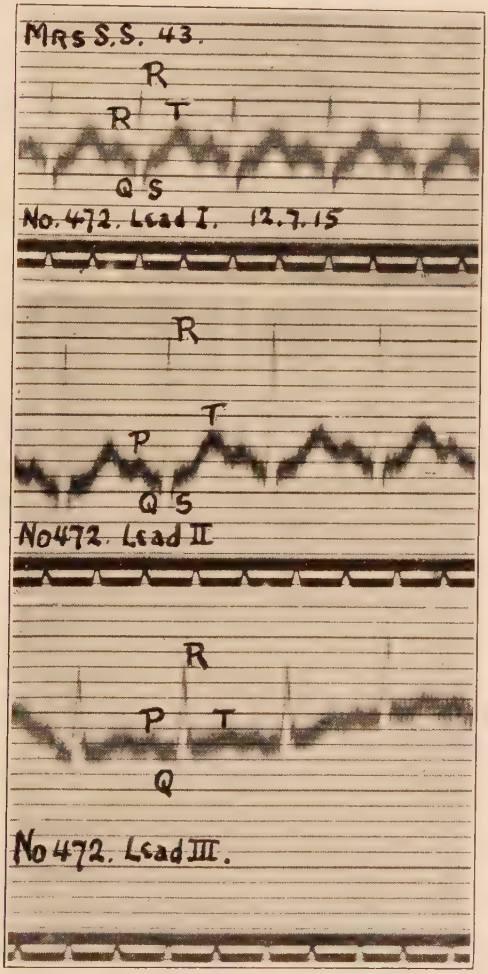

Fig. 14.—Case 43. Electrocardiograms of S. S., showing lessened *T* wave after operation that persisted for at least six months after operation.

in this clinic, although we cannot subscribe to "the converse proposition that if the summits fall within the normal limits of amplitude the heart is probably normal." We have seen in 2 cases

of this series, as well as in several other cardiac cases examined electrocardiographically, that the electrocardiogram was well within normal limits shortly before death from cardiac failure, and that

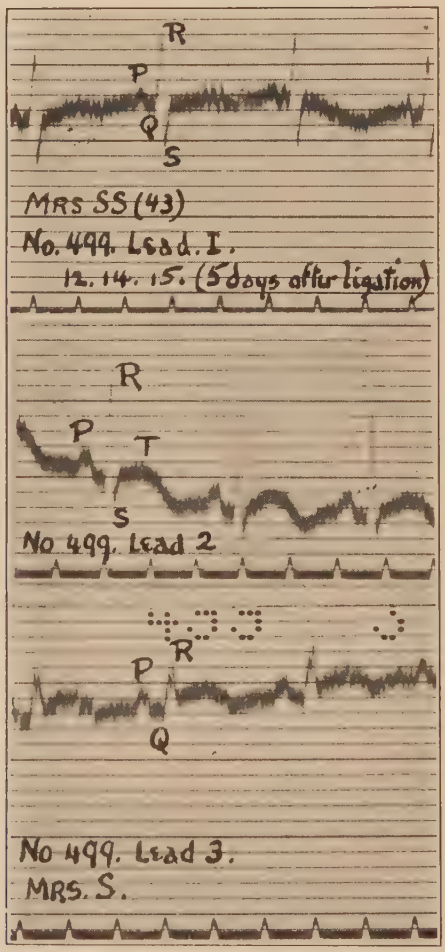

Fig. 15.—Same case as Fig. 14.

even the form of the complex might be nearer normal shortly before or during acute cardiac failure than it had been when the patient was clinically in better condition.

TABLE 2.—ELECTROCARDIOGRAPHIC DATA ON GOITRE PATIENTS

No.	Preoperative electrocardiogram.			Postoperative electrocardiogram.			
	Rate	P-R Int.	Form of egg.	Time after.	Rate	P-R Int.	Form of egg.
1	114	0.14	Normal	6 wks.	120	0.14	S less in all leads.
2	130	0.11	T_2 and T_3 inverted	7 days	109	0.14	S increased in all leads. T less (inverted or upright).
3	130	0.14	T_2 and T_3 inverted				
4	66	0.22	L. V. H.	5 days	78	0.20	P and T less in all leads.
				3 mos.	72	0.22	Same.
5	60	0.18	R. V. H.	4½ mos.	80	0.12	R. V. H. much less marked.
6	90	0.12	T_2 diphasic, T_3 inverted	5½ mos.	80	0.12	T_1 diphasic, T_2 and T_3 inverted. Not improved.
7	89	0.18	S_2 and S_3 very large.				
8	95	0.22	Tendency to L. V. H.				
9	98	0.14	Normal	7 days	100	0.14	T less in all leads.
10	68	0.14	Normal				
11	150	0.12	Q_2 and Q_3 very large.	5 days	112	0.16	T less in all leads.
12	127	0.16	Normal				
13	73	0.15	T_1 and T_2 diphasic	7 days	125	0.16	All T_2 inverted, Q_2 and Q_3 increased.
..	..	..	.....	3 mos.	95	0.14	Same. Died two days after second operation.
14	102	0.16	Normal	8 days	111	0.18	Very little change, Q_2 more marked S_2 less so.
15	58	0.16	Normal	7 mos.	68	0.16	Same. One ventricular extrasystole recorded.
16	88	0.14	Big notch low on R_3	3 days	109	0.14	S less in all leads. Notch on R_3 less and higher.
17	120	0.15	Tendency to R. V. H.	9 days	125	0.14	Tendency to R. V. H. more marked.
18	96	0.14	Deep S in all leads	8 days	105	0.14	No change.
19	130	0.14	Normal	3 mos.	108	0.13	No change.
20	87	0.14	Tendency to L.V. H.	9 days	100	0.14	L. V. H. more marked.
21	130	0.14	Tendency to R.V. H.	8 days	125	0.14	R. V. H. more marked.
22	103	0.14	T_2 and T_3 inverted	....	..	..	Died two days after operation.
23	66	0.16	Tendency to R.V. H.	5 mos	68	0.14	Less tendency to R. V. H. T waves increased.
24	..	..	.....	5–7 yrs.	120	..	Auricular fibrillation, ventricular extrasystoles R. V. H. constant.
25	93	0.15	Tendency to R.V.H. Sinus arrhythmia	9 days	94	0.15	Less tendency to R. V. H. Sinus arrhythmia less.
26	..	..	.....	2–4 yrs.	127	varying	Auricular flutter. A–V Block (2 : 1–4 : 1).
27	100	0.13	L. V. H.	5 days	130	0.14	L. V. H. unchanged. T_1 and T_2 less marked.
28	90	0.14	L.V.H. T_1 negative	1 yr.	..	..	L.V.H. unchanged. T_1 upright.
29	100	0.17	Tendency to L.V.H.	9 mos.	..	..	L. V. H. more marked.
30	102	0.16	Normal	8 days	90	0.16	Less T.
31	100	0.15	Tendency to L.V H.	6 days	109	0.15	Tendency to L. V. H. less marked.
32	103	0.16	L. V. H.				
33	120	0.14	Tendency to R.V.H. T_2 and T_3 inverted	6 days	90	0.13	T less in all leads. R. V. H. unchanged.
34	117	0.14	Normal	7 days	88	0.14	S and T in all leads.
35	102	0.11	Tendency to R.V.H.	8 days	110	0.12	No change.
36	105	0.15	Normal	4 days	130	0.16	No change.
37	118	0.14	Tendency to R.V. H. Notched P_3 sinus arrhythmia	4 mos.	107	0.16	Less tendency to R. V. H. Notch in P_3 absent.
38	140	0.12	R. V. H. T_3 inverted	1 yr.	134	0.12	T_1 and T_2 increased T_3 less, R. V. H. no change.
39	75	0.18	Normal	3 days	102	0.16	T less in all leads.
40	101	0.14	Tendency to R.V.H.	....	..	..	Died 24 hours of heart failure.
41	63	0.16	L. V. H.	4 days	66	0.18	Less T in all leads.
42	102	0.16	Tendency to L.V.H.	6 wks.	80	0.18	L. V. H. more marked.
43	146	0.11	Normal R_3 notched	3 days	102	0.12	T less in all leads. R_3 notched deeply at peak.
44	130	0.12	Normal	8 days	94	0.14	S increased; T less in all leads.
45	109	..	Auricular fibrillation T_2 diphasic, T_3 inverted	....	..	..	Improved without operation AF constant.
46	..	..	.....	5 mos.	64	0.14	Normal.
..	..	..	.....	1 yr.	60	0.14	S increased in all leads.
47	105	0.14	R. V. H.	7 days	115	0.15	R. V. H. disappeared. Normal.
48	..	..	.....	9 days	88	0.12	Normal.
49	127	0.14	Occasional ventricular extrasystole	7 days	130	0.14	Less T in all leads. No extrasystoles seen.
50	90	0.17	L. V. H. Occasional ventricular extrasystole	....	..	..	Improved without operation.
51	85	..	Auricular fibrillation T_2 diphasic, T_3 inverted R_3 M shaped	No operation	..	..	Improved without operation. Normal rhythm developed coincident with general improvement. T_2 upright. R_3 still anomalous.

R. V. H. and L. V. H. refer to right and left ventricular preponderance respectively.

Preoperative variations from the normal form of the ventricular complex, notice of which has been included in Table II under the heading of "Form of Egg," not only include such changes as those showing hypertrophy of one or other ventricle, but also notchings

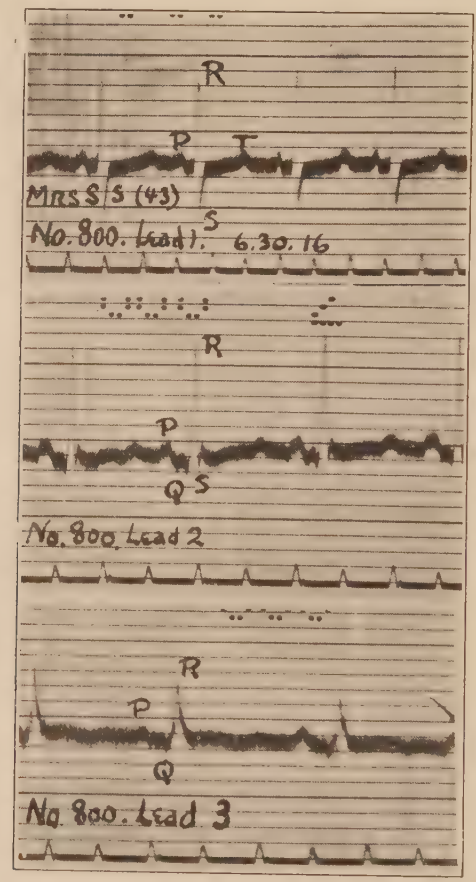

FIG. 16.—Same case as Fig. 14.

and undue prominence of single waves of the Q, R, S group (the clinical significance of which changes is as yet unknown) and also various changes in form of the T wave. Essentially normal electrocardiograms in both form and rhythm were found in 22 of the 51 cases of the series.

Hypertrophy of Auricles and Ventricles. Although the electrocardiogram registers action currents whose intensity depend on the

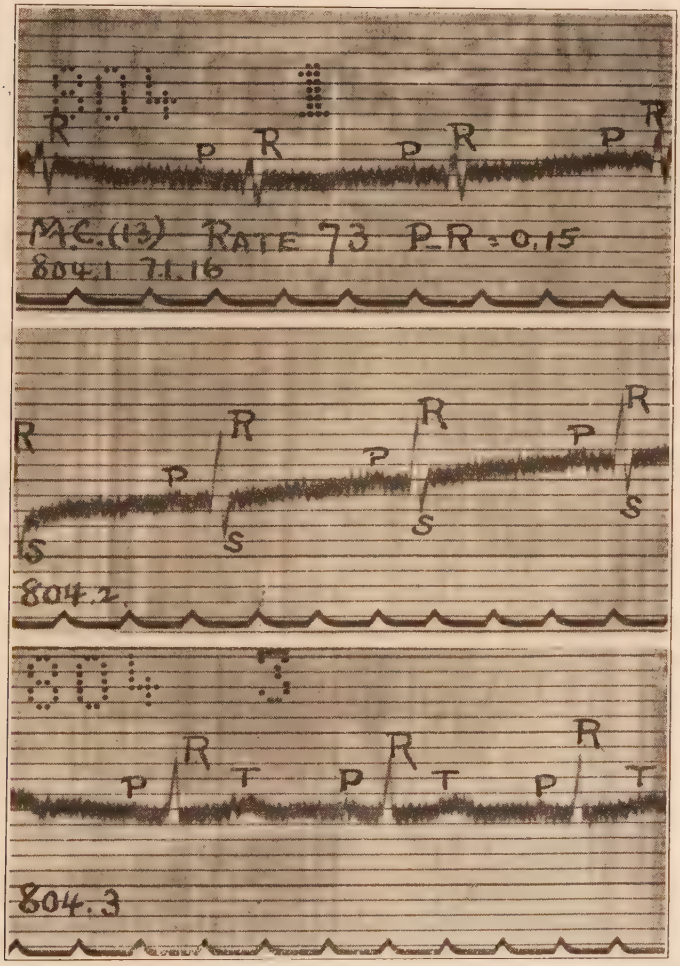

FIG. 17.—Case 13. Electrocardiograms of M. C., showing development of a negative *T* wave after operation. That this may be considered as a bad prognostic indication is supported by the death of this patient from cardiac failure after a second operation.

strength of stimulus production, certain characteristic changes in the form of the ventricular complex have been recognized as indicating a preponderating hypertrophy of one or other ventricle. The

evidence as to hypertrophy that is obtained in this way is more accurate and reliable than either the results of percussion or ortho-

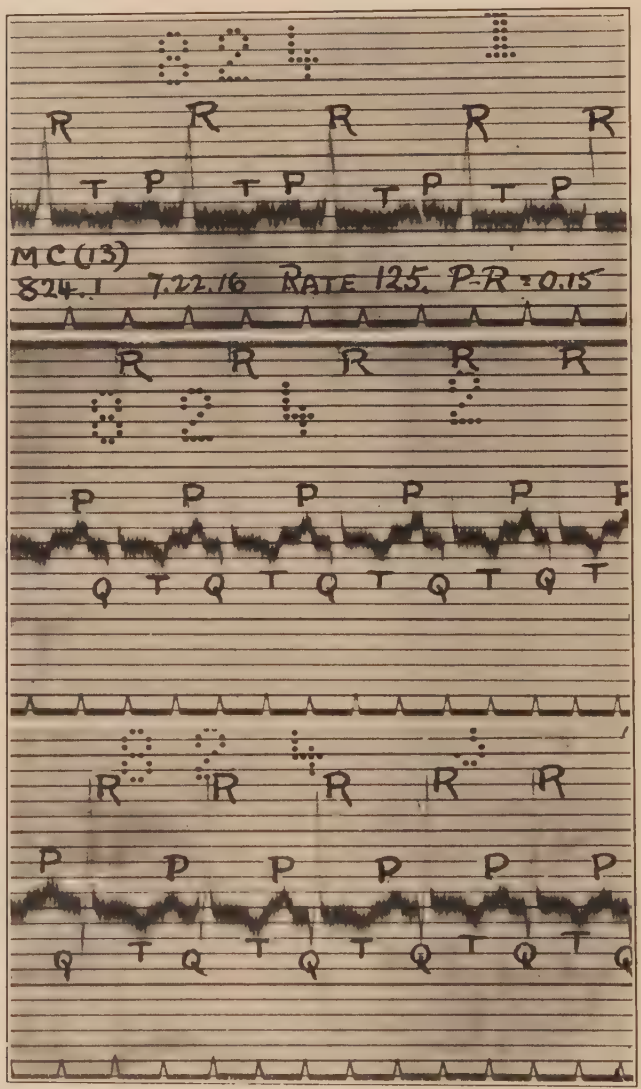

FIG. 18.—Same case as Fig. 17.

diagraphic examination. The deduction as to the size of the muscle mass is nearly always true, because the stimulus going to

the hypertrophied muscle mass is nearly always correspondingly increased. Some of the cases of this series, however, and also experi-

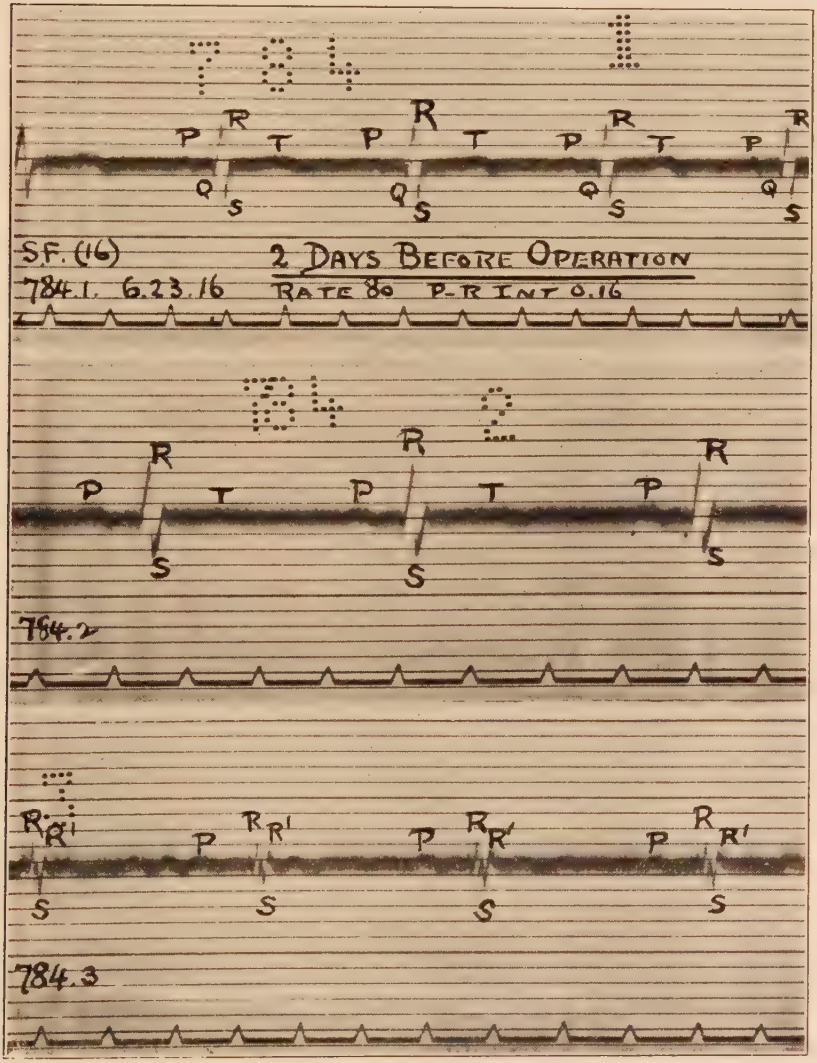

FIG. 19.—Case 16. Electrocardiograms of S. F., taken two days before, three days after, and twelve days after surgical operation, showing approximation of R_3 to normal in the last records. Note that the deep notch of R_3 in the first records becomes less and less noticeable in the second and third records. In this case the small postoperative T wave had already become larger by the twelfth day.

mental work still in progress, indicate that the form of the ventricular complex (*i. e.*, the intensity of the stimulus production)

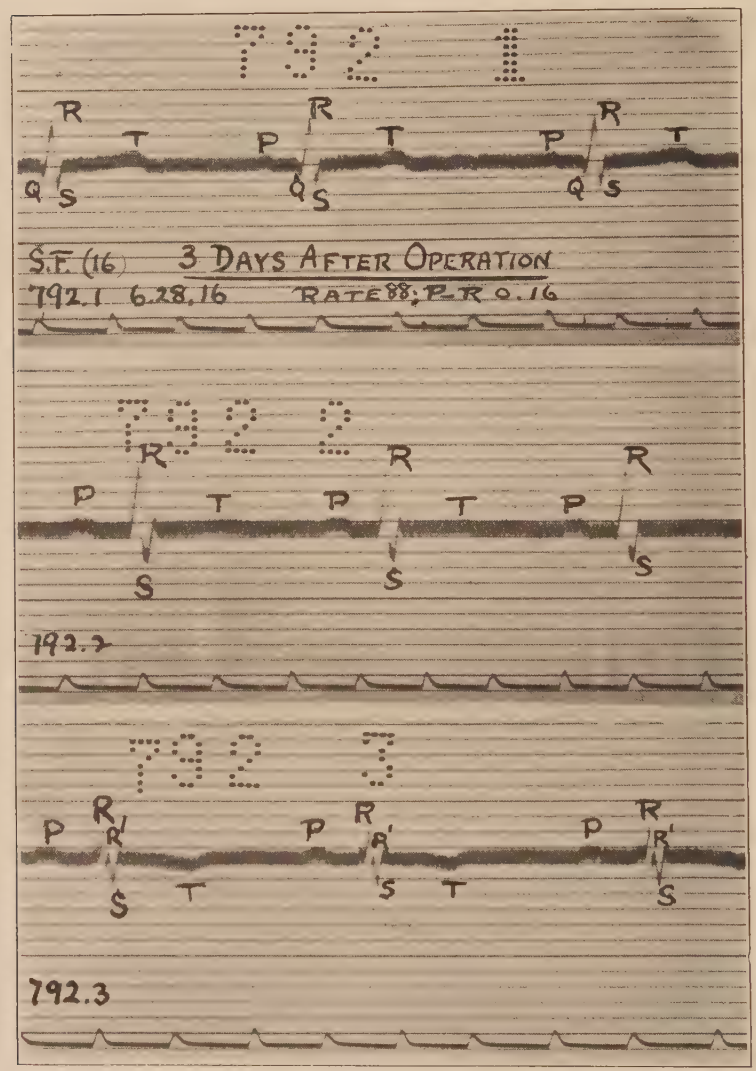

FIG. 20.—Same case as Fig. 19.

may be noticeably changed without the occurrence of equivalent change in muscle mass. Such alterations occurring within a few

days after operation, when it would have been impossible for the muscle mass to have changed materially, have been indicated in

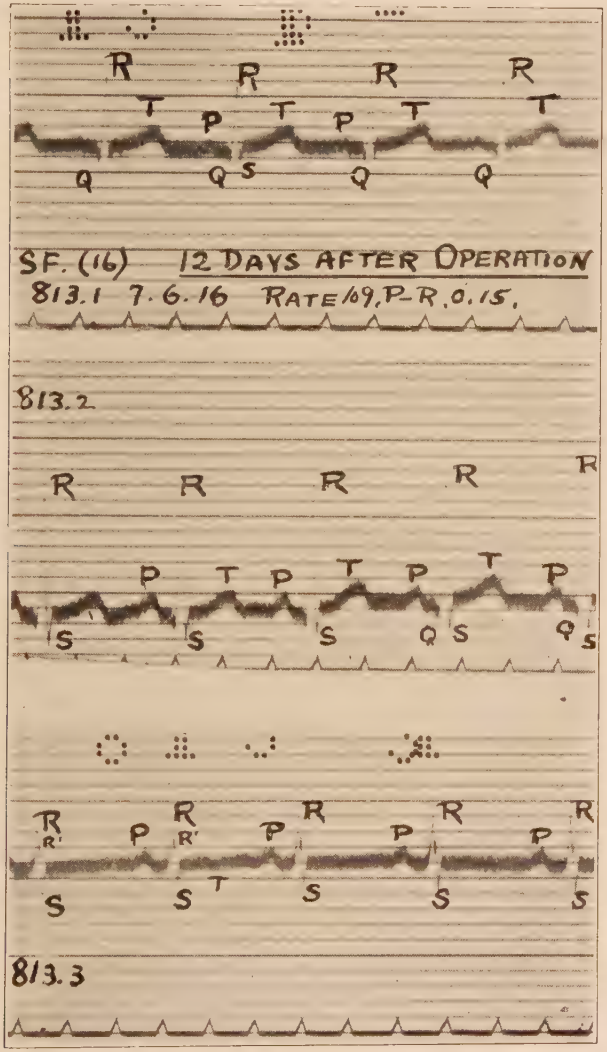

FIG. 21.—Same case as Fig. 19.

Table II. The change in form that follows change in the axis of the heart has been shown to be relatively slight and clinically negligible, and is therefore not considered in this series.

The state of right ventricular preponderance (R. V. H.) has been considered as present when both the S wave of Lead I (S_1) is greater than the R wave of Lead I (R_1), and when R_3 is greater than R_2

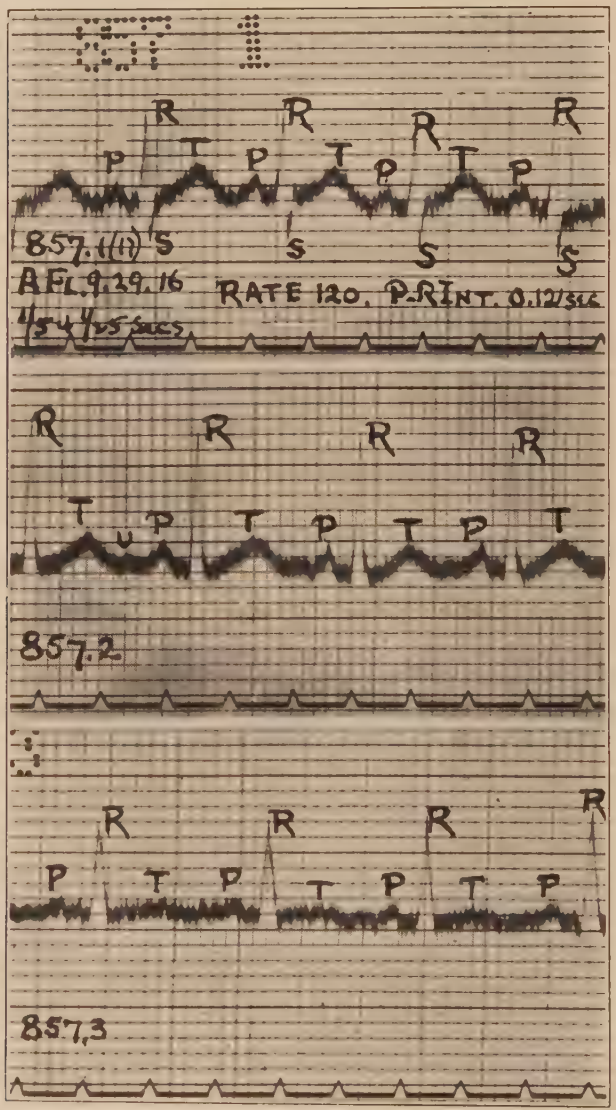

Fig. 22

and when Q_2 and Q_3 are unusually large. When one of these factors is present or when the waves in question approach equality

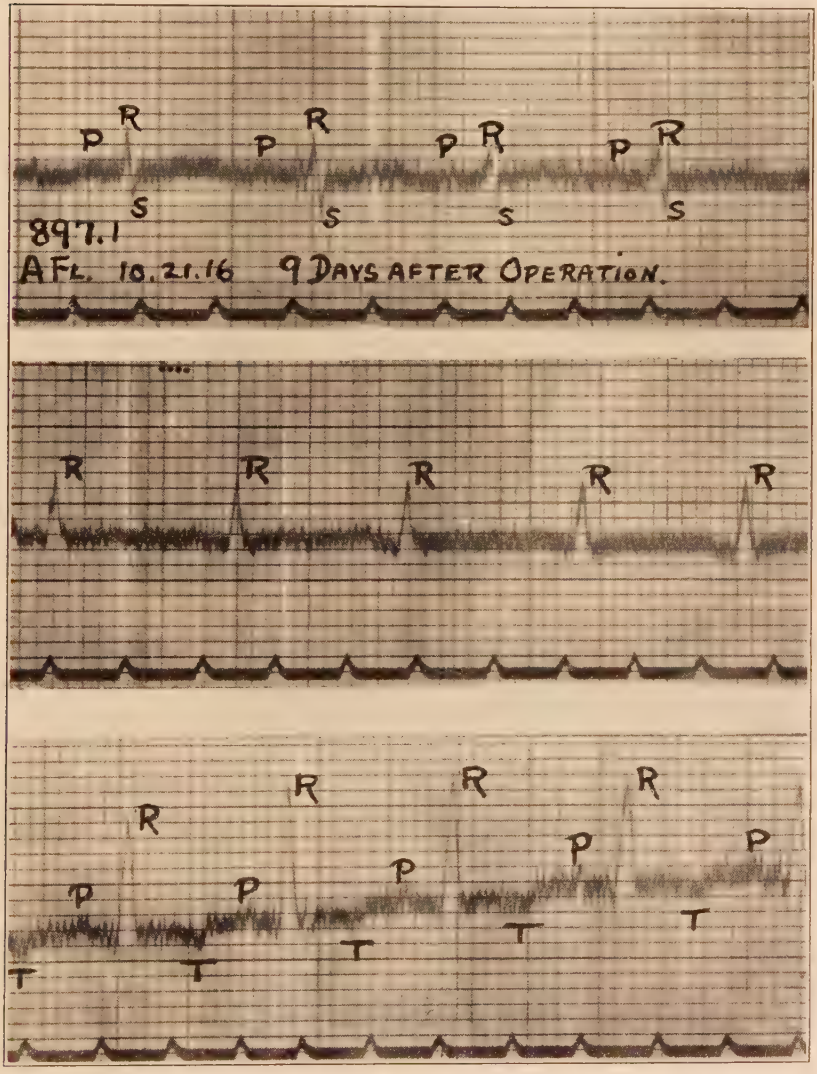

FIG. 23

the condition is spoken of as a "tendency to R. V. H." Similarly when R_1 is greater than R_2 and S_3 greater than R_3 and Q_1 promi-

nent the state of left ventricular preponderance is recognized, and when this condition is approximated it is spoken of as a "tendency to left ventricular preponderance."

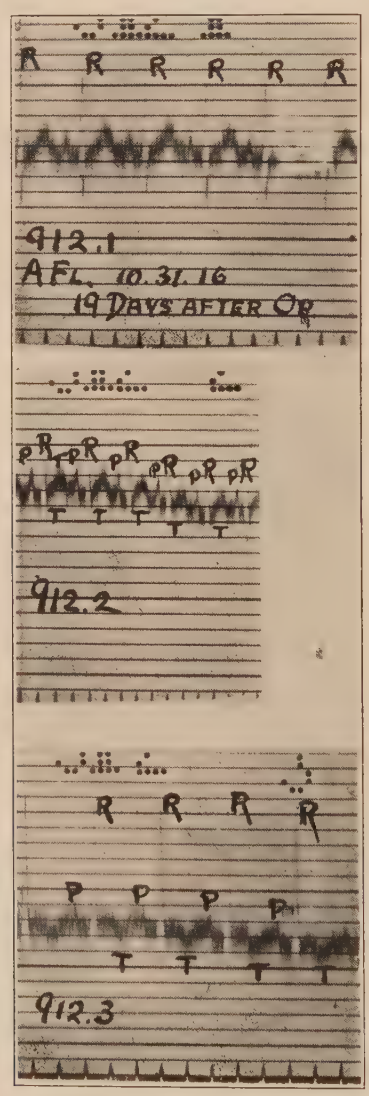

FIG. 24

In the present series the majority of cases betrayed no signs of ventricular hypertrophy in the electrocardiogram. This is in accord with the experiences of other writers. Contrary to the general opinion, however, when hypertrophy was present, right ventricular preponderance has proved to be as common as left. It was distinct in 3 cases and a tendency to it existed in 8 cases. Left ventricular preponderance occurred in 6 cases and a tendency to it in 5 cases. It is difficult to explain why some cases of uncomplicated toxic goitre should develop right and others left ventricular preponderance. The most probable explanation would be that the left preponderance is due to whatever causes are responsible for the increased systolic pressure; whereas in the right preponderance cases other factors, such as relatively or actually incompetent mitral valve, would be considered as playing a more important part. Some significance may be attached to the fact that the average duration of the disease in the right ventricular cases was under two and a half years, whereas in the left ventricular cases it was over four and a half years.

After surgical operation 5 of the right ventricle cases showed less preponderance, 3 showed no appreciable change, and 2 an increased amount. Of the L. V. H. cases after operation, on the other hand, 4 showed no change, 6 showed an increased amount, and only 1 showed a lessened degree of preponderance. This probably indicates that the left ventricular cases are due to a muscular hypertrophy that has already been accomplished and cannot be relieved by treatment even though signs of improvement are present. The same reasoning may be applied to those right ventricular cases that do not change or progress. For those that showed lessened hypertrophy after operation a lessened impulse due to diminution of the intoxication might be assumed or possibly a nearer approach to competency of the mitral valve.

Changes in T Wave. In most of the cases of this series the T wave was well developed. This was especially noted in the more toxic cases and was even true in the 5 cases in which T_2 was either diphasic or inverted and in both cases in which T_1 was diphasic or inverted. If in the absence of digitalis medication the T wave may be considered, as many authorities believe, as an index of the force

of the cardiac contraction, such a result would be expected from the overacting goitre heart.

It is significant that out of the 23 cases that were examined within ten days of operation 11 showed a distinctly lessened T wave in all leads, coincident with general clinical improvement. One case also that improved greatly without operation exhibited a diminished *T* wave in all leads during the improved period. The welcome deduction that could be drawn from these facts, to wit, that the smaller postoperative *T* wave indicated a quieting down of the overactive heart, was unfortunately complicated by another observation, namely, that three control studies of three normal hearts showed the same tendency to a postoperative diminution of the *T* wave. This is a detail that in itself needs further investigation; at present, however, we are limited to the statement that such diminution is less in the normal than in the goitre cases and only lasts a few days. The diminution of the *T* wave of the goitre heart is so much more accentuated and durable, often lasting three or more months, that it may be taken as highly probable that the heart's overaction has really been lessened and the treatment been proved beneficial in so far as the electrical changes may be taken as a guide.

The persistent postoperative inversion of the *T* waves in one case (Case 13), with a subsequent fatal outcome to a second operation, has already been commented upon. In another case (Case 6) a failure to improve after operation was accompanied by the development of a negative *T* wave. In 2 other cases (Cases 28 and 51) general improvement during observation was accompanied by a change from negative to positive *T* waves. To this extent support is given to the idea that inverted *T* waves are of bad prognostic significance.

Other Changes in Form of the Ventricular Complex. In the form of the preoperative electrocardiograms various small changes from the established normal have been observed such as would be found in any similar series of cardiac cases. I refer to such details as unusually deep *S* waves in one or more leads, notching of the *R* wave and so forth. These were frequently changed after operation, or appeared after operation when they had previously been absent.

As the significances of such changes, however, is not yet understood, and as they were often contradictory, no deductions can be drawn from them. Thus in Case 1 the *S* wave of an otherwise normal record was decreased in all leads after operation; whereas in Case 2 the *S* waves were all increased after operation. Case 16 (Fig. 11) presents an item of interest. In the preoperative electrocardiogram the *Q*, *R*, *S* group of Lead III wasa bizarre collection of three upward and two downward peaks. Three days after operation, while the patient's general condition was improving, Lead III showed these peaks in such modified form that they could be explained as a deep notching of an *R*, *S* group. Nine days later, coincident with further improvement, Lead III had almost approached a normal complex, the notch being higher on the *R* wave and barely visible. While such anomalies are common in Lead III, and while their underlying cause is unknown, nevertheless it is reasonable to assume that the nearer approach of the electrocardiogram to a normal form is indication of an improvement in the cardiac mechanism.

Summary. 1. Electrocardiographic studies have been made of 51 cases of goitre, mostly of the toxic type, in as many cases as possible both before and after surgical operation.

2. In the series of 47 patients that submitted to surgical operation (ligation, partial excision, and enucleation of adenomata) 3 deaths occurred; 2 of these offered no premonitory signs in either clinical or electrocardiographic examination; in the third case the development of negative *T* waves might have served as an adequate warning.

3. Electrocardiograms, essentially normal as to form and rhythm, were found in 22 cases (43 per cent.). Preponderating hypertrophy of the right ventricle (or a tendency thereto) was found in 11 cases, and of the left ventricle (or a tendency thereto) also in 11 cases. After operation, however, one-half of the right ventricular cases showed a diminished degree of preponderance, whereas all but one of the left ventricular cases showed either no change or an increased amount of preponderance.

4. Cardiac arrhythmia was found as follows: sinus arrhythmia, 4 cases; ventricular extrasystoles, 3 cases; auricular fibrillation,

3 cases; auricular flutter, 1 case; delayed conductivity, 2 cases. Two of the cases of fibrillation and the case of flutter proved constant over several years. The other case of fibrillation was of the transient kind and disappeared coincident with the improvement that followed medical treatment.

5. The *T* wave was found to be unusually prominent in most cases. In about half the cases it was markedly and persistently diminished after operation. This was found to be true to a lesser degree in postoperative cases with normal hearts. Other changes in form of the ventricular complex after operation indicated an approximation to normal cardiac mechanism.

6. Blood-pressure estimation showed an increased pulse pressure in most cases that was diminished with the improvement that followed surgical relief. Systolic pressure was also high in those cases that showed left ventricular preponderance, but never exceeded 170 mm. Hg.

Conclusions. 1. In early cases of toxic goitre the characteristic tachycardia is not accompanied by any signs of myocardial change that are demonstrable with the string galvanometer.

2. With persisting overaction of the heart, hypertrophy of either ventricle may become manifest.

3. Progressive hypertrophy and overaction results in myocardial degeneration that may be manifested by any type of cardiac irregularity: sinus arrhythmia, premature contractions, auricular flutter, auricular fibrillation, heart-block, etc.

4. If the existing intoxication is the chief factor in the production of the arrhythmia this may disappear with removal of the intoxication.

5. Successful treatment, whether medical or surgical, improves the cardiac condition by this means. This is shown not only by the occasional disappearance of an arrhythmia but also by diminution in the size of the T wave and in the pulse-pressure as well as by the general clinical condition.

6. The development of diphasic or inverted *T* waves, especially in Leads I and II, should probably be considered as influencing prognosis unfavorably.

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STUDIES OF LUNG VOLUME

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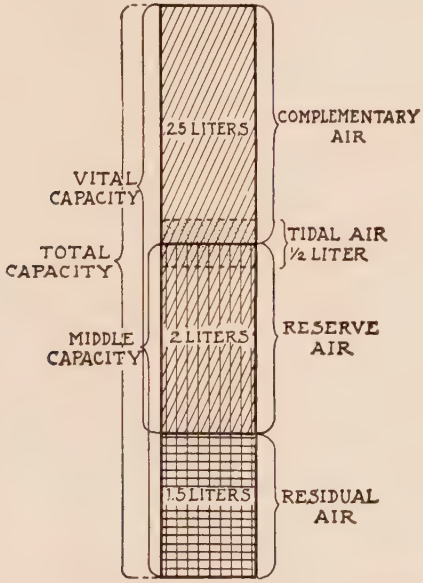
Definition of Terms. The amount of air a person is able to expire after a maximum inspiration is called "vital capacity" (Hutchinson, 1846). The vital capacity does not, however, indicate all the air within the lungs. A certain quantity remains even after a maximal expiration; we call this "residual air" (Davy, 1800). The sum of the vital capacity and the residual air, *i. e.*, the total volume of air held by the completely filled lungs, is called the "total capacity" or "total lung volume."

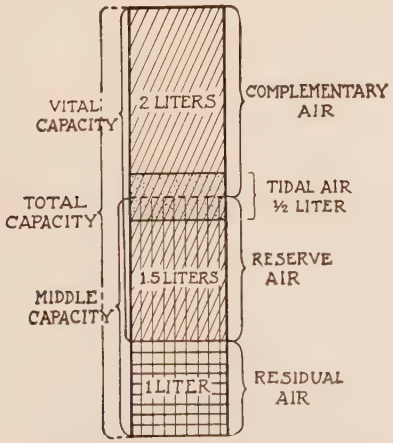
If one stops breathing half-way between a normal inspiration or a normal expiration, there will be in the lungs a certain quantity of air greater than the residual air and less than the total capacity (Text-figs. 1 and 2). We call this amount of air the "middle capacity" (Panum, 1868). The difference between the total capacity and the middle capacity (all that can be breathed in after a half-expiration) is called the "complementary air." The difference between middle capacity and residual air (all that can be breathed out after a half-expiration) is called the "reserve air."

In accordance with the definition now in use, the vital capacity is equal to the sum of the reserve and complementary air. Under normal conditions the difference between the inspiration and expiration (the tidal air) is much less than the vital capacity, and can approximately be estimated at 500 c.c. This means that a person only uses 250 c.c. of his reserve air and 250 c.c. of his complementary air in normal breathing. The rest of the vital capacity is to be considered as a reserve which can be used if necessary

under abnormal conditions. There is a striking contrast, however, between the reserve air and the complementary air, the



TEXT-FIG. 1.—Approximate lung volumes for average normal man.



TEXT-FIG. 2.—Approximate lung volumes for average normal woman.

former always being within the chest and the latter always being outside the chest under normal resting conditions (Hutchinson).

METHODS FOR DETERMINING LUNG VOLUMES. The vital capacity, the tidal air, the reserve air, and the complementary air can be determined by means of a calibrated, easily movable spirometer. In determining the residual air, however, it is necessary to apply a more complicated method. It is usually determined by having the subject expire completely until only the residual air is left in the lungs. He then inspires from a bag or spirometer containing a known amount of nitrogen, oxygen, or hydrogen, which he mixes with the air in his lungs by respiring from five to seven times. Then the mixture is analyzed and the amount of residual air calculated from the degree to which the air in the chest has diluted the gas in the bag or spirometer. The total capacity and the middle capacity can be determined either directly by the bag alone, or indirectly by adding the residual air to the vital capacity and the reserve air respectively, as determining with a spirometer. We have, in our work, determined all the figures by means of the mixing method and later on checked the vital capacity by means of a spirometer.

TABLE I.—Summary of Lung Volume Determinations on Normal Individuals

No. of individual.	Name.	Age.	Height.	Weight.	Bag.						Spirometer.	
					Residual air.	Middle capacity.	Total capacity.	Vital capacity.	Reserve air.	Complementary air.	Vital capacity.	
											Expiration.	Inspiration.
		yrs.	cm.	kg.	liters.	liters.	liters.	liters.	liters.	liters.	liters.	liters.
1	Dr. P.	34	185.0	90.0	2.48	4.80	8.22	5.74	2.32	3.42	5.90	5.70
2	Dr. J.	31	179.0	76.0	2.10	4.70	8.05	5.95	2.60	3.35	5.95	5.70
3	Dr. Do.	29	186.0	86.0	1.86	..	7.20	5.34	..	..	..	..
4	Dr. F.	32	178.0	68.0	1.87	3.89	6.51	4.64	2.02	2.62	4.90	4.85
5	Dr. S.	32	178.0	91.0	1.47	3.45	6.24	4.77	1.98	2.79	4.87	4.80
6	Dr. D.	34	178.0	69.5	1.52	3.66	6.13	4.61	2.14	2.47	4.65	4.60
7	Dr. C.	29	172.5	65.0	1.46	3.31	5.88	4.42	1.85	2.57	4.63	4.55
8	Dr. A.	38	165.0	67.0	1.61	3.50	5.58	3.97	1.89	2.08	3.87	3.77
9	Dr. M.	32	167.5	63.0	1.25	2.99	4.95	3.70	1.74	1.96	3.97	3.93
10	Dr. Mo.	29	162.5	51.0	1.41	2.60	4.56	3.15	1.19	1.94	3.40	3.35
11	Dr. K.	28	152.0	52.0	1.53	2.23	3.84	2.31	0.70	1.61	2.40	2.35
12	Mrs. S.	34	175.0	88.0	1.64	2.88	5.10	3.46	1.24	2.22	..	..
13	Miss G.	26	173.0	63.0	1.42	3.17	5.05	3.63	1.75	1.88	3.75	3.70
14	Mrs. H.	24	162.0	59 0	1.07	2.69	4.91	3.84	1.62	2.22	3.90	3.85
15	Miss C.	23	169.0	65.0	1.10	2.40	4.12	3.02	1.30	1.85	3.15	3.10
16	Miss L.	29	156.0	43.0	1.15	2.45	3.93	2.78	1.30	1.48	2.75	2.70
17	Mrs. A.	28	158.0	52.0	0.97	2.28	3.93	2.96	1.31	1.65	3.10	2.95
18	Miss D.	21	160.0	53.0	1.15	2.35	3.72	2.57	1.20	1.40	2.65	2.60

Immediately after the determination of the lung volumes the chest measures of the subject were taken.

Lung Volumes in Eighteen Normal Individuals. The results of our experiments on 18 normal persons between twenty and thirty-eight years of age are tabulated in Table I, and diagrams of the same determinations are shown in Text-fig. 3. The values for the different lung volumes in these determinations agree with what other investigators have found.

From his determinations on 8 normal men and 4 normal women, Bohr derived a standard for the different lung volumes which is usually accepted.

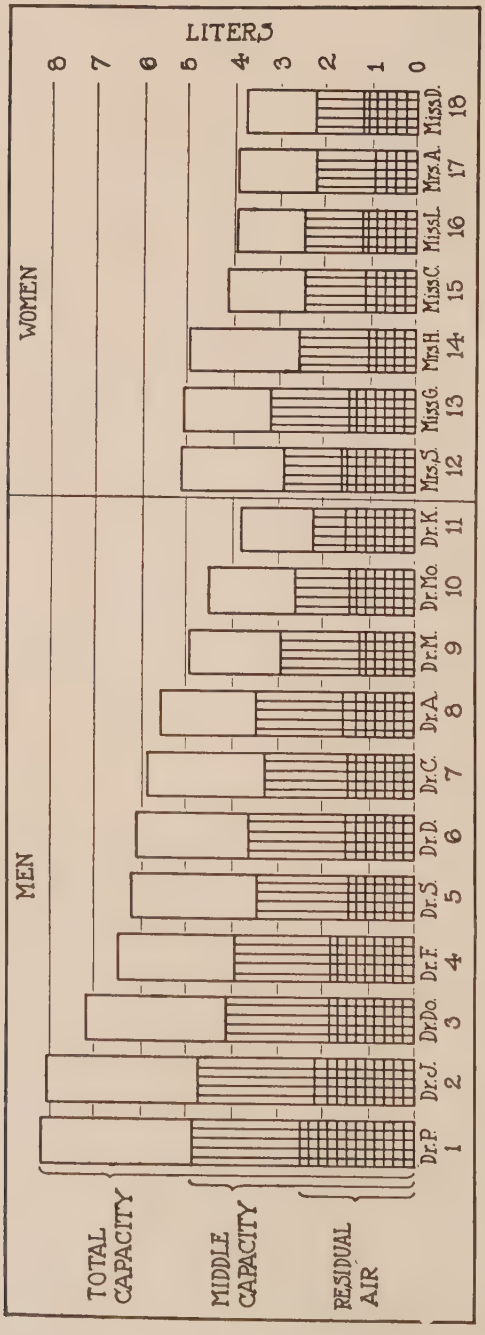
We have divided our results into two groups according to the sexes and believe that the figures given in Table II and Text-figs. 1 and 2 represent the approximate average somewhat more closely than the approximations used by Bohr; namely, 1 liter of residual, 2 liters of reserve, and 2 liters of complementary air.

Table II.—Average Lung Volumes for Normal Men and Women in Standing Position

Sex.	Residual air.	Reserve air.	Mean.	Complementary air.	Total capacity.
	liters	liters	liters	liters	liters
Men	1.5	2.0	3.5	2.5	6.0
Women . . .	1.0	1.5	2.5	2.0	4.5

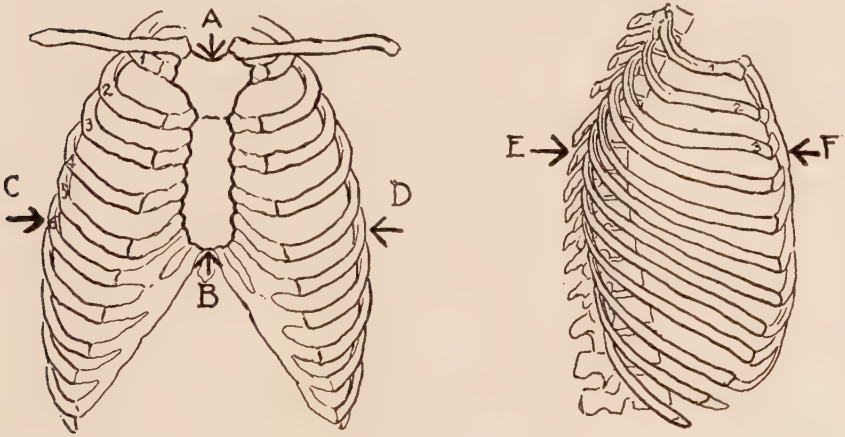
Previous Investigations to Find a Relationship between the Vital Capacity and Other Body Figures. Pulmometry has never played an important part in clinical medicine, chiefly on account of the great variations in the lung volumes of different persons. For that reason we have been unable to tell whether the lung volume in a pathologic case is normal or not for the individual examined unless the deviation from the usual values is great. The variations in the values of the lung volume in different individuals have been recognized by even the earliest investigators.

Determination of the "Chest Volume" and Calculations of a Ratio between Chest Volume and Lung Volume in Different Positions of the Chest (Full Inspiration, Rest, and Full Expiration). The problem of finding an accurate relationship between the lung volume and chest or body size was unsolved.



TEXT-FIG. 3.—Chart showing the lung volumes in eleven normal men and seven normal women.

It seemed to us, however, that it might be possible to approach the solution by using the chest volume as the constant and the lung volume as the variable. The reason for this seems obvious when we consider the chest wall as a sort of spirometer. When a person is respiring from a spirometer, it is a natural thing to look upon the chest wall as another spirometer connected with the first one and moving inversely to the latter. And if we take different individuals it is natural to regard their chests as spirometers containing different amounts of air.



TEXT-FIG. 4.—Points on the thorax where the chest measurements are taken. *A B* is the height of the chest, *C D* the breadth, and *E F* the depth.

After some consideration and experiments we came to the following procedure which has been used in all our cases. The height of the chest is taken as the length of the sternum from incisio intraclavicularis to a point just below articulatio sternoxiphoida. The depth is then taken as the horizontal distance from the middle of the sternum at the insertion of the third rib to the spinal column, and the breadth is the distance across the sixth ribs in the midaxillary line. The points between which the measures are taken are almost without any muscular covering. The transverse points are in the axilla between musculus pectoralis major and musculus

latissimus dorsi. The distances representing the depth and breadth vary with the phases of inspiration; the height is constant (Text-fig. 4).

The measuring requires some practice and a good deal of care. We do it in the following way: The person stands in a natural position. The points are found and marked. The point on the upper part of the sternum is rather easy to find; it is just above the edge of the bone. The lower point is sometimes very difficult to locate. We do it as follows: The curvature is found and lines are drawn to indicate it. Then we try to find the joint between the sternum and processus xiphoideus. It is usually slightly prominent. The point from which we measure is just below that prominent ridge. Locating the tip of the processus xiphoideus sometimes helps, but it cannot always be done. The lateral points are easy to find by counting the ribs. In taking the measure it is necessary to put the nodes of the pelvimeter tight to the chest wall in order to get as close to the bone as possible. It is particularly necessary to take care that the ends of the pelvimeter do not slip and go into the intercostal spaces. The first measures are taken in rest (half-way between normal expiration and inspiration, middle capacity). The pelvimeter is kept on and the person is requested to take a maximum inspiration and stop a second while the measures are taken. Then he is asked to expire to the residual air and stop for another measurement. The product of the figures obtained does not, of course, represent the real chest volume, but a volume approximately proportional to it.

In Table III are given the data on different normal individuals. The product of the measurements in the three dimensions is given as the chest volume and the ratio between the chest volume and lung volume calculated as

$$\frac{100 \times \text{lung volume}}{\text{chest volume.}}$$

The average ratio for the total lung capacity is 55, for the middle capacity 37, and for the residual air 19.

TABLE III.—Summary of Thorax Measurements in the Three Positions of Respiration, namely, Expiration, Rest, and Inspiration, and Ratios of Chest Volumes Calculated from These Measurements to Lung Volumes

No. of individual.	Name.	Position of chest.	Sternum.	Diameter.		Chest volume.	Lung vol.	Ratio, 100 × lung volume / chest volume.
				Ant-post.	Transverse.			
			cm.	cm.	cm.	liters.	liters.	
1	Dr. P.	Expiration	22.0	21.0	29.5	13.63	2.48	18.2
		Rest	22.0	22.0	31.0	15.00	4.88	32.0
		Inspiration	22.0	24.0	32.5	17.15	8.22	48.0
2	Dr. J.	Expiration	21.0	17.5	29.0	10.65	2.10	19.7
		Rest	21.0	19.5	30.5	12.49	4.70	37.6
		Inspiration	21.0	21.0	32.0	14.08	8.05	57.2
3	Dr. Do.	Expiration	20.5	17.0	29.5	10.28	1.86	18.1
		Rest	20.5	18.5	30.0	11.36	4.63	..
		Inspiration	20.5	20.0	32.0	13.12	7.20	54.8
4	Dr. F.	Expiration	19.5	18.5	26.0	9.38	1.87	19.9
		Rest	19.5	19.0	28.0	10.38	3.89	37.5
		Inspiration	19.5	20.0	30.0	11.70	6.51	55.6
5	Dr. S.	Expiration	18.0	18.5	27.5	9.15	1.47	16.1
		Rest	18.0	19.5	28.5	10.00	3.45	34.5
		Inspiration	18.0	20.0	30.5	11.00	6.24	56.7
6	Dr. D.	Expiration	20.5	18.5	24.5	9.30	1.52	16.4
		Rest	20.5	19.5	25.5	10.20	3.56	35.9
		Inspiration	20.5	21.5	26.5	11.45	6.13	53.6
7	Dr. C.	Expiration	19.5	17.5	27.5	9.39	1.46	15.6
		Rest	19.5	18.5	28.0	10.10	3.31	32.6
		Inspiration	19.5	20.0	29.5	11.50	5.88	51.1
8	Dr. A.	Expiration	20.0	16.0	24.5	7.83	1.61	20.6
		Rest	20.0	17.0	25.0	8.50	3.50	41.2
		Inspiration	20.0	18.0	27.5	9.90	5.88	56.4
9	Dr. M.	Expiration	19.5	15.5	26.0	7.86	1.25	16.4
		Rest	19.5	16.0	26.5	8.26	2.99	36.4
		Inspiration	19.5	17.0	27.5	9.11	4.64	51.0
10	Dr. Mo.	Expiration	19.0	15.0	22.0	6.27	1.41	22.5
		Rest	19.0	16.0	23.0	6.99	2.60	37.4
		Inspiration	19.0	18.0	24.5	8.38	4.56	54.6
11	Dr. K.	Expiration	16.0	14.5	24.0	5.57	1.53	27.5
		Rest	16.0	15.0	24.5	5.88	2.23	37.9
		Inspiration	16.0	17.0	25.0	6.80	3.84	56.4
12	Mrs. S.	Expiration	17.5	18.5	24.5	7.93	1.64	20.7
		Rest	17.5	19.0	25.2	8.38	2.88	34.3
		Inspiration	17.5	20.2	27.5	9.72	5.10	52.4

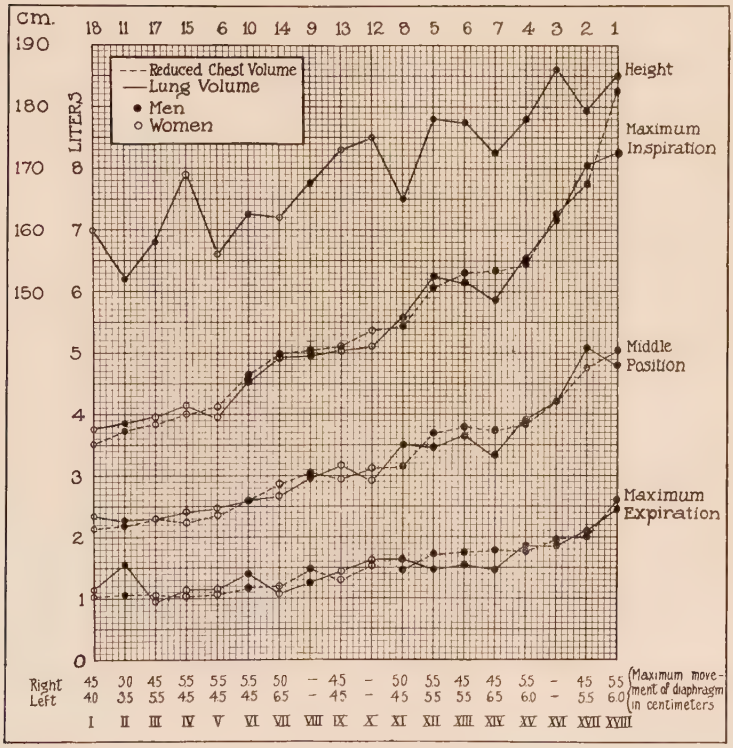
TABLE III.—Continued

No. of individual.	Name.	Position of chest.	Sternum.	Diameter.		Chest volume.	Lung vol.	Ratio, 100 × lung volume / chest volume.
				Ant. post.	Transverse.			
			cm.	cm.	cm.	liters	liters	
13	Miss G.	Expiration	18.3	14.8	25.3	6.85	1.42	20.7
		Rest	18.3	16.5	26.1	7.88	3.17	40.3
		Inspiration	18.3	18.5	27.3	9.29	5.05	54.2
14	Mrs. H.	Expiration	17.2	16.0	24.8	6.83	1.07	15.7
		Rest	17.2	17.1	25.8	7.77	2.69	34.6
		Inspiration	17.2	18.3	28.3	8.91	4.91	55.1
15	Miss C.	Expiration	17.9	13.9	22.2	5.52	1.10	19.9
		Rest	17.9	14.9	22.6	6.03	2.40	39.7
		Inspiration	17.9	15.7	25.8	7.25	4.12	55.8
16	Miss L.	Expiration	17.1	14.9	22.5	5.73	1.15	20.0
		Rest	17.1	16.0	23.4	6.40	2.45	38.3
		Inspiration	17.1	17.3	25.3	7.49	3.93	52.4
17	Mrs. A.	Expiration	16.2	14.0	23.5	5.32	0.97	18.2
		Rest	16.2	15.5	24.5	6.15	2.28	37.1
		Inspiration	16.2	17.1	25.4	7.04	3.93	55.4
18	Miss D.	Expiration	17.1	14.0	22.1	5.30	1.15	21.7
		Rest	17.1	15.0	22.2	5.79	2.35	40.3
		Inspiration	17.1	16.5	23.2	6.55	3.72	57.8

The curves of Text-fig. 5 show the different chest volumes multiplied by these factors (reduced chest volume). It will be seen that there is a close agreement between the reduced chest volumes and the actual lung capacities. We have plotted the height on the upper part of the chart to show that the relations between the different lung volumes and the height are much more variable than the relations between the lung and chest volumes. The relationship between height and vital capacity (Hutchinson) is equally variable. The vital capacity, on the other hand, bears nearly as constant a ratio to the reduced chest volume as do the total or middle capacities. The average ratio between the vital capacity and the middle chest volume is 45 (Table IV).

EXCURSIONS OF THE DIAPHRAGM. Realizing that the measurement of the chest wall does not give us the variations in the height of the thoracic cavity, we have made a particular study of the move-

ment of the diaphragm by means of x-rays.[1] The figures are given in Table IV. It will be seen that there is one man with a very small



TEXT-FIG. 5.—Chart showing air contents of lungs (lung volumes) in normal subjects as determined in the three respiratory positions by the dilution method (solid lines) and as calculated from the thoracic measurements (broken lines). The subjects are arranged in order according to chest volumes measured at maximum inspiration. The numbers above the chart are those by which the same subjects are designated in Text-fig. 3. The numbers below indicate the maximum excursion of the right and left diaphragm in centimeters, as calculated from fluoroscopic tracings.

movement of his diaphragm. His residual air is unusually great (Text-figs. 3 and 5). He apparently expired naturally so far as the

[1] We used fluoroscopy. Being unable to use parallel light we worked out a correction for the parallax by measuring the distance from the light to the screen (50 cm.) and the distance from the light to the middle part of the diaphragm (35 cm.). The correction is very close to 0.7 in all instances; for that reason all our directly found values have been multiplied by that factor.

thoracic movement was concerned, but was unable to press his diaphragm up at the end of the expiration. He was a physically untrained man, with rather undeveloped abdominal musculature. A too small movement of the diaphragm might, of course, indicate that he was unable to lower it during inspiration. The normal figures for his total capacity and the abnormally high figure for his residual air prove that this was not the case. One of the women (No. 14, Table III and Text-fig. 3) had a particularly small residual ratio, 15.7. It will be seen that the movement of her diaphragm is very extensive. She had been trained in college to breathe very deeply and had powerful abdominal muscles. She wore, like all the other women, a rather loose corset during the determination. The importance of the movements of the diaphragm will be discussed more in a later paper.

TABLE IV.—Maximum Excursions of the Right and Left Diaphragm

No. of individual.	Name.	Greatest possible movement of diaphragm.			100 × residual air / chest volume at expiration	100 × vital capacity / chest volume at rest
		Right.	Left.	Right + left.		
			Men			
		cm.	cm.	cm.		
1	Dr. P.	5.5	6.0	11.5	18.2	38.3
2	Dr. J.	4.5	5.5	10.0	19.7	47.7
3	Dr. Do.	..	..	..	18.1	47.0
4	Dr. F.	5.5	6.0	11.5	19.9	43.0
5	Dr. S.	5.5	5.5	11.0	16.1	47.7
6	Dr. D.	4.5	5.5	10.0	16.4	45.2
7	Dr. C.	4.5	6.5	11.0	15.6	43.7
8	Dr. A.	5.0	4.5	9.5	20.6	46.7
9	Dr. M.	..	..	..	16.4	44.8
10	Dr. Mo.	5.5	4.5	10.0	22.5	45.1
11	Dr. K.	3.0	3.5	6.5	27.5	39.2
			Women			
12	Mrs. S.	..	..	..	20.7	41.3
13	Miss G.	4.5	4.5	9.0	20.7	46.1
14	Mrs. H.	5.0	6.5	11.5	15.7	49.4
15	Miss C.	5.5	4.5	10.0	19.9	50.1
16	Miss L.	5.5	4.5	10.0	20.0	43.5
17	Mrs. A.	4.5	5.5	10.0	18.2	48.1
18	Miss D.	4.5	4.0	8.5	21.7	44.4

SUMMARY. 1. The total capacity, middle capacity, and residual air have been determined on 11 normal men and 7 normal women. All the determinations have been done on subjects in standing position and at least two hours after a meal.

2. The figures for the total and middle capacities agree with those of previous investigators; namely, with Bohr's. The values for the residual air seem to be a little higher than those previously published.

3. A procedure has been devised by means of which it has been possible to find a relation between external chest measurements and lung capacity.

4. With the aid of the relationship thus ascertained the lung capacity normal for a chest of given measurements can be estimated.

5. The excursions of the diaphragm have been studied.

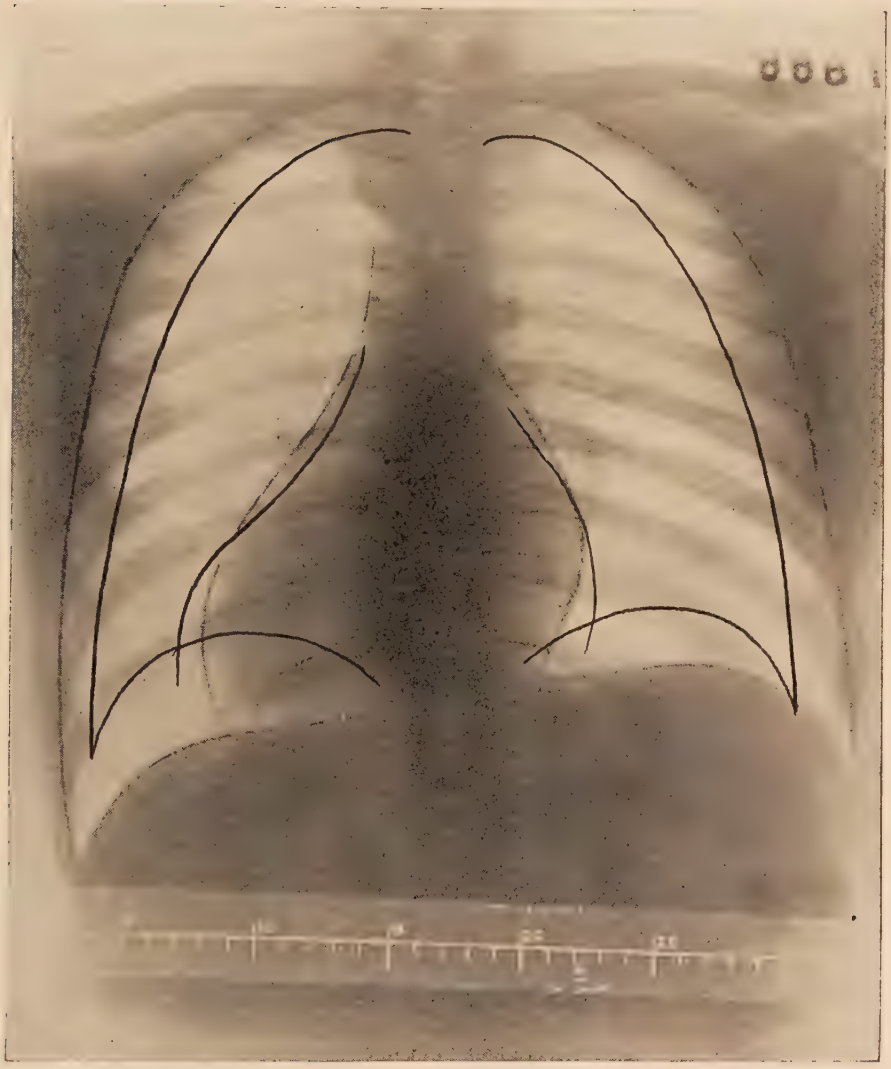
DISCUSSION

DR. COLE said: It was hoped that this method might be used in estimating the amount of lung volume involved in cases of pneumonia. For technical reasons, however, it is difficult to make observations on patients as ill as pneumonia patients are likely to be. During the early stages of the disease, however, and also during convalescence, such observations can be made and it is hoped that at such times the method will give us considerable information.

DR. LUNDSGAARD said: Dr. Cole has asked me to tell how the different lung volumes are measured. I think I can do that in a few words. The vital capacity is measured by means of an easily movable recording spirometer into which the person performs a maximal expiration after a full inspiration. The rest of the air in the lungs—the residual air—can never be brought out of the lungs, and we are therefore unable to apply direct measurements to that part of the lung volume. We are compelled to measure it indirectly, which can be done just in the same way as we determine that part of an Ewald test meal which we cannot take up by means of the rubber tube. For that purpose a known amount of neutral reacting water is mixed with an unknown amount of stomach content of a known acidity. From the degree of dilution we calculate the amount of residual stomach content. Thus in the same way, a definite amount of pure oxygen (2 liters), enclosed in a rubber bag, which can be connected with the mouth of the person, is mixed with an unknown amount of residual air with a known percentage (79 per cent.) of oxygen. From the degree of dilution the amount of residual air is easily calculated. The residual air added to the vital capacity is the total lung volume.

A

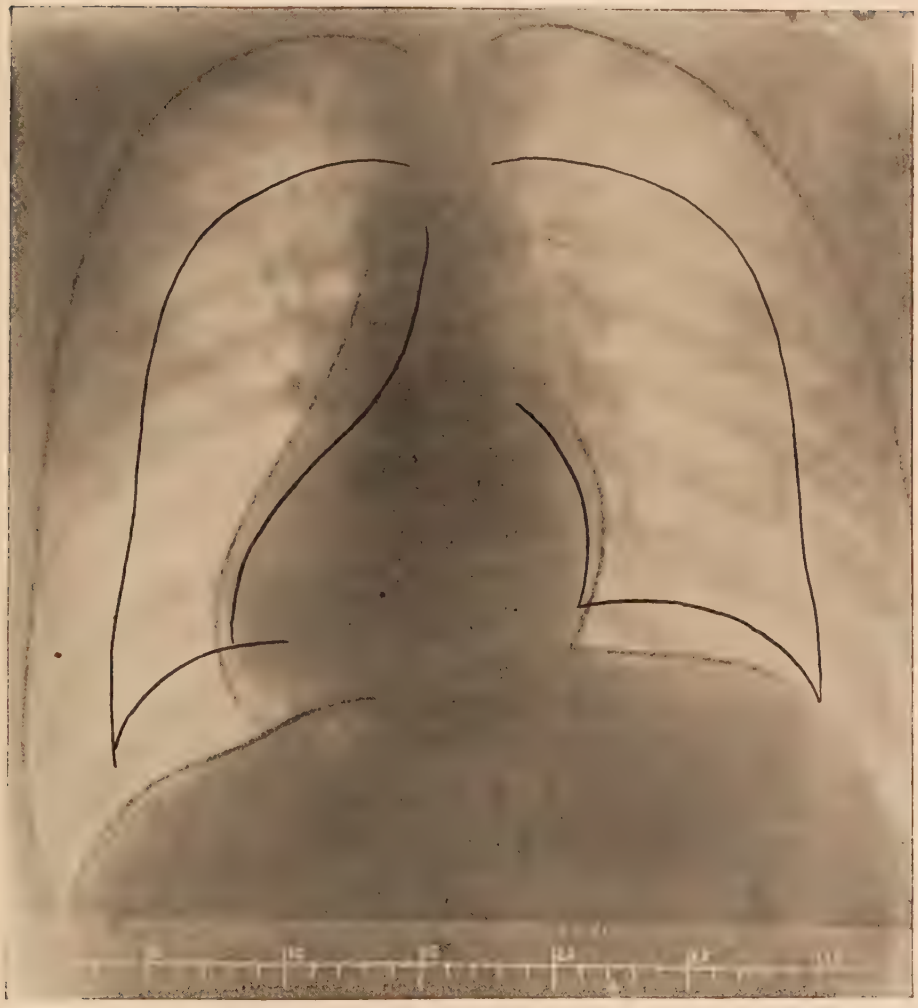
Two *x*-ray pictures from a normal man, No. 7, taken after maximum expiration (*A*) and maximum inspiration (*B*). The outline of *A* is superimposed on *B*.



B

A

Two *x*-ray pictures from No. 11 (*A*) and No. 1 (*B*). They are both taken in maximum inspiratory position. *A* is superimposed on *B*.



B

FROZEN SECTIONS FROM A CASE OF STERNUM-ERODING AORTIC ANEURYSM

By GEORGE W. NORRIS, A.B., M.D.

AND

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The case here reported is, we believe, unique in the following respects:

1. Photographs were obtained showing the gradual growth of the protruding mass.

2. Frozen sections were made showing the intrathoracic relations as they existed during life.

3. The exact site of rupture and mode of death are actually depicted in a more vivid manner than could be done by a regular autopsy.

4. The hydrothorax, the pulmonary atelectasis, and the extreme dyspnea are explained in a manner which by another method of study would be far less satisfactory, if at all possible.

W. F., aged fifty years, negro, stevedore by occupation, was admitted to the Pennsylvania Hospital in February, 1916, in the service of Dr. J. Norman Henry, complaining of pain in the sternal region and in the upper extremities, associated with dyspnea.

Family History. Revealed nothing of importance.

Personal History. Measles, whooping cough, mumps as a child. Has had night-sweats. Highest weight, 256 pounds; usual weight, 230 pounds; present weight, 171 pounds. With the exception of constipation there were no gastro-intestinal symptoms. Patient is unmarried; has worked as a stevedore for many years, using alcohol in considerable quantities. Had Neisserian infection at the age of thirty-five; lues at the same time.

Present Illness. In September, 1913, three and one-half years ago, the patient noticed indigestion and began to have pain in the sternal region, shortness of breath, restlessness at night. In August, 1914, he noticed a slight bulging of the upper portion of his chest. Previous to this he had been treated in various hospitals and dispensaries without apparent benefit. In June, 1915, he was treated at the Polyclinic Hospital with injections of salvarsan. He derived more benefit from this than from any other treatment. Notwithstanding, however, the bulging of the upper chest continued to increase. In December, 1915, he had an attack of "influenza," which caused an aggravation of all his symptoms. Ever since then he has had paroxysms of coughing and choking of sufficient severity to cause insomnia.

Physical Examination. General: Well-nourished, well-developed adult male, lying comfortably in bed, showing no dyspnea or evidence of cardiac or respiratory embarrassment.

Head and Neck: Head large, with heavy, coarse features. Pupils equal, and react to light and accommodation. Ocular movements full, conjunctivæ muddy, slightly jaundiced. Nose and ears negative. Tongue thick, heavily coated; teeth in bad condition, several molars missing. Considerable pyorrhea. Throat chronically inflamed. Moderate visible pulsation of vessels of neck. Postcervical glandular enlargement.

Respiratory System. In region of upper half of the sternum there is a prominent hemispherical bulging mass measuring transversely across the summit 19.5 cm., longitudinally across summit 14.5 cm., which pulsates visibly with beat of heart, and on palpation is found to be expansile in character. A diastolic shock is felt over the mass.

The thorax is otherwise large, well-developed and seemingly symmetrical. Expansion fair; seems equal. Note on percussion clear at apices and over bases. Over mass at upper sternal region there is dulness throughout, extending laterally to middle third of the left clavicle. Breath sounds are clear; no rales.

Posteriorly the lungs seem clear and resonant throughout, excepting the area at the level of the scapular spines in midline, where there is definite dulness on percussion and diminished voice sounds.

Circulatory System. Pulse regular, greater volume in left arm than right. Blood-pressure: right arm, 130 to 85; left arm, 190 to 100. Pulse in the right arm slightly delayed. No marked pulsation over precordium. Apex beat in sixth interspace 14 cm. to left of midsternal line. No murmurs at mitral area. Heart sounds distant, muffled, feeble. Over the mass at base of the heart there is heard a soft, systolic blowing murmur and a short, sharp, diastolic second sound. Similar sounds are heard along the course of the axillary artery on right side but not on left.

Abdomen: Full, rounded, soft. No tenderness or rigidity. Liver dulness 4 cm. below costal margin. The spleen was not felt.

Extremities: Reflexes present; seem increased. Legs and arms large, well developed, symmetrical.

Urine examination at times showed a trace of albumin and a few hyalin casts. Wassermann reaction was negative.

X-ray examination (Dr. Bowen): Fluoroscopic only. "This man has a large aneurysm, presumably of the arch of the aorta. The shadow is nearly symmetrical in the median line; pulsates on both sides. In lateral view the shadow is circular, or nearly so, in front, and posteriorly is lost in the spine."

The patient was discharged from hospital "condition unchanged," in May, 1916 (Fig. 1).

FIG. 1

He was readmitted in August, 1916 (service of Dr. Arthur Newlin), having been fairly comfortable until the middle of July. Five or six weeks previous to the present admission a small elevation was noticed near the central part of the already large bulging pulsating area of the upper sternum. Orthopnea and insomnia were severe. Large doses of morphin were necessary to produce even reasonable comfort. The aneurysm had definitely increased in size, and at its central portion showed a small area of softening, through which a thin, sanguineous serum was constantly oozing (September 30, 1916). At the time of last admission the globular area on the chest measured 14 x 20.5 cm. It now measures 21 x 23 cm. and pulsates visibly, especially over the protruding central core. His voice is somewhat husky. The breath sounds over the left side of the chest are suppressed; on the right side the breath sounds are vesicular and

associated with crackling rales. The temperature ranges between normal and 104° F., being distinctly hectic in type. He is now constantly in a state of orthopnea and spends most of the time leaning forward, resting his head and elbows on his knees. On October 6 the left pleural cavity was aspirated and 660 c.c. of clear amber fluid were withdrawn. A Wassermann examination was again made and found negative.

Fig. 2

A second fluoroscopic examination was reported by Dr. Bowen as follows:

"The aneurysm does not appear larger in the fluoroscope than it does clinically; that is, it does not appear to widen out within the chest. There

is, however, in the left chest a shadow which is continuous with that of the aneurysm, and is sufficiently dense to block out all detail. I believe this represents a considerable collection of fluid in the left pleura; but I am unable to discover how much of the shadow is fluid and how much is aneurysm."

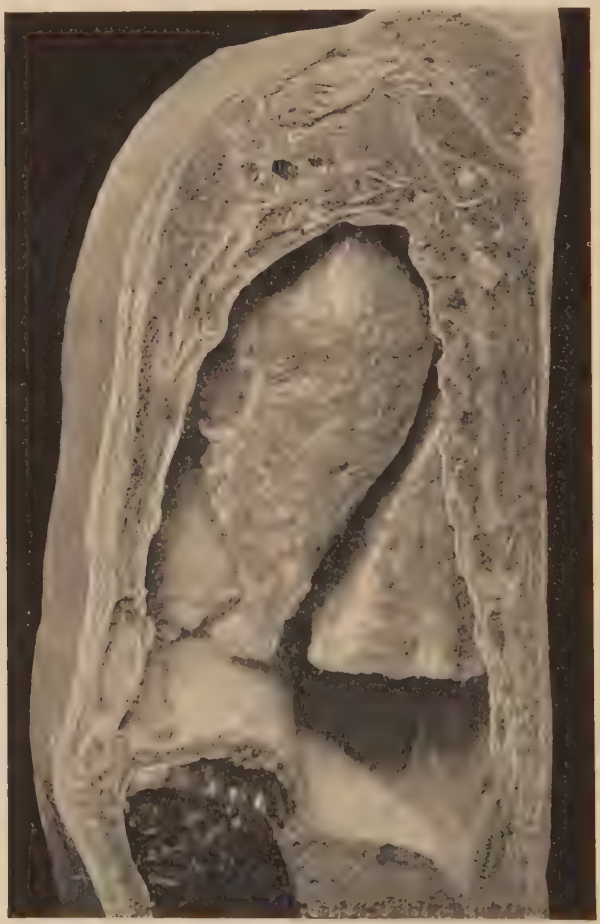

FIG. 3

October 12, 1916, the patient, having been more or less constantly under the influence of morphin, was seized at 10.30 A.M. with violent hemorrhage from the mouth and nose, and expired in two or three minutes. Death was believed to have been due to rupture of the aneurysm into a bronchus.

Instead of a regular autopsy the body was frozen in a horizontal, dorsal position and prepared in the usual manner. Sections about two inches in thickness were then cut serially in an anteroposterior plane, beginning on the left side. Upon removing the first slab containing the ribs the pleural cavity was exposed as shown in Fig. 2.

FIG. 4

Fig. 2. The left pleural cavity is filled with frozen serum, the lung, which is atelectatic, is seen at two points, and the stomach is filled with frozen blood clot. The diaphragm is depressed downward, more so posteriorly over the liver than anteriorly over the stomach. It forms an almost

horizontal plane, the dome being practically obliterated. A portion of the left hepatic lobe comes into view.

Fig. 3 depicts the pleural cavity after removal of the serum and shows the pericardium and atelectatic lung. On the anterior surface of the upper lobe is a long, fibrous scar which, upon section, was found to extend

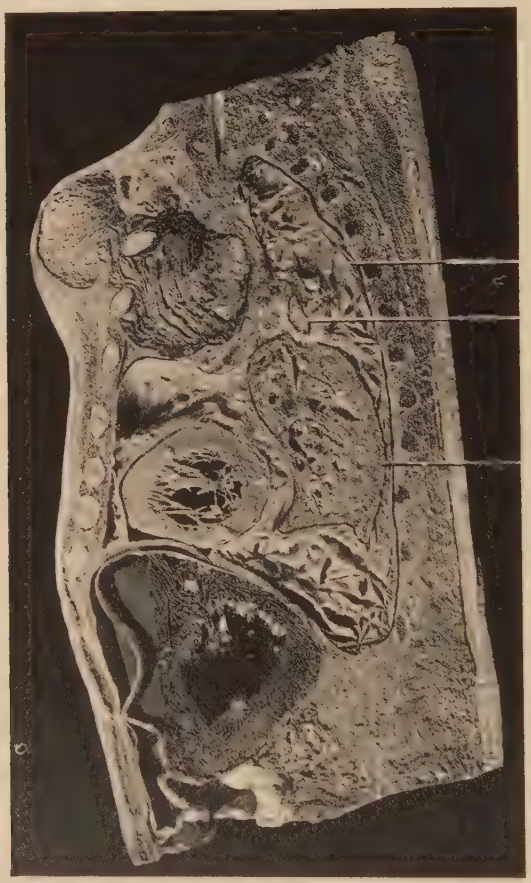

Fig. 5.—*F. S.*, frozen serum in pleural cavity; *D. A.*, dilated aorta; *A. L.*, atelectatic lung.

into the pulmonary parenchyma to the depth of about 1 cm. The lung above this scar, and also at the extreme upper portion of the left apex, was adherent to the costal pleura. There was nothing in the patient's past history nor in the gross appearance of the tissue to elucidate the nature of the lesion. The aneurysmal protrusion of the anterior chest wall is shown in both Figs. 2 and 3.

Fig. 4 shows the obverse side of section three after the removal of the frozen serum from the pleural cavity, the blood clots from the pulmonary vessels and the aneurysm and the pus from the bronchi. The patient's hectic temperature may have resulted from absorption of pus from the bronchi. The hour-glass form of aneurysm is well illustrated, and this

Fig. 6.—*F.*, fascia; *E. S.*, eroded sternum (no sac); *C. P.*, calcified pericardium; *R. V.*, right ventricle; *B. F.*, bronchial bifurcation; *L. B.*, left bronchus; *A.*, aorta; *L. A.*, left auricle; *A. V.*, aortic valve; *L. V.*, left ventricle; *E.*, esophagus filled with blood.

section shows plainly the point at which the aneurysm after burrowing through the deep tissues of the chest wall emerged and expanded as a subcutaneous structure. Just below the aneurysmal sac is a calcified, enlarged lymph node.

Fig. 5, the next section, shows to an extreme degree the pulmonary

atelectasis; the bronchi were filled with purulent material. The aneurysm, which is seen to be filled with firmly organized, laminated blood clot, protrudes outward above and below the first rib. It must not be assumed that the aneurysm originally made its way out between the first and second ribs. This portion was reached by lateral encroachment after a passage had been made through the sternum. After thawing out the clot was found to have the consistency of a stiffened sponge. Its interstices were filled with blood and serum. The pericardial sac immediately below the aneurysm was densely calcified. A portion of the left ventricle is shown with its columnæ carneæ and one papillary muscle. The whole heart lies much more horizontally than is normally the case. Its walls are thickened.

Fig. 6 depicts a section through the middle of the sternum and the spinal column, and shows the spinal cord severed in the median line. The aneurysm now appears in its largest dimensions. Only a small portion of the entire sac is freely open as a blood channel, although the blood, and more especially the serum, did seep through the interstices of the clot and break through the skin of the anterior chest wall. At the posterior portion of the sac one sees the point of rupture, the location at which the aneurysm has ulcerated into the left bronchus. There is no direct communication between the aneurysm and the esophagus. The blood, which nearly fills the stomach and the lower portion of the esophagus, was coughed up and swallowed, a process which must have been going on for some time before death, since the latter was very sudden and apparently the result of suffocation. It will be noted that the tracheal bifurcation is nearly filled with blood (Fig. 7).

The flattened mass of tissue immediately behind the aneurysm, between the point of rupture and the trachea, contains the left bronchus and the esophagus. The occlusion of the former explains the atelectasis of the left lung. The sternum is completely eroded. The manubrium and part of the gladiolus have been entirely absorbed. The latter projects upward into the aneurysm as naked, roughened bone; no sac is interposed between these two structures, although a portion of the deep fascia and perhaps the periosteum remain intact, the aneurysm forming a secondary sac outside of them.

The large dimensions of the aneurysmal sac indicate the extent to which the left recurrent laryngeal nerve must have been attenuated and stretched and readily account for the husky voice of the patient.

Fig. 7 illustrates many of the statements made in the description of the preceding figure. In this section the bronchial bifurcation is filled with blood clot. A portion of the flattened esophagus is visible. The heart and liver are displaced downward and the lumen of the pulmonary artery and vein is greatly encroached upon. As a result of pressure the left auricle has lost its normal ovoid shape and is distinctly flattened in its

anteroposterior diameter. This applies particularly to the upper part, where the pressure of the aneurysm would be exerted to the greatest extent, and involves the ostia of entrance of the left pulmonary veins into the auricle. The encroachment upon these structures accounts for the left-sided hydrothorax. The great thickness of the left ventricular wall

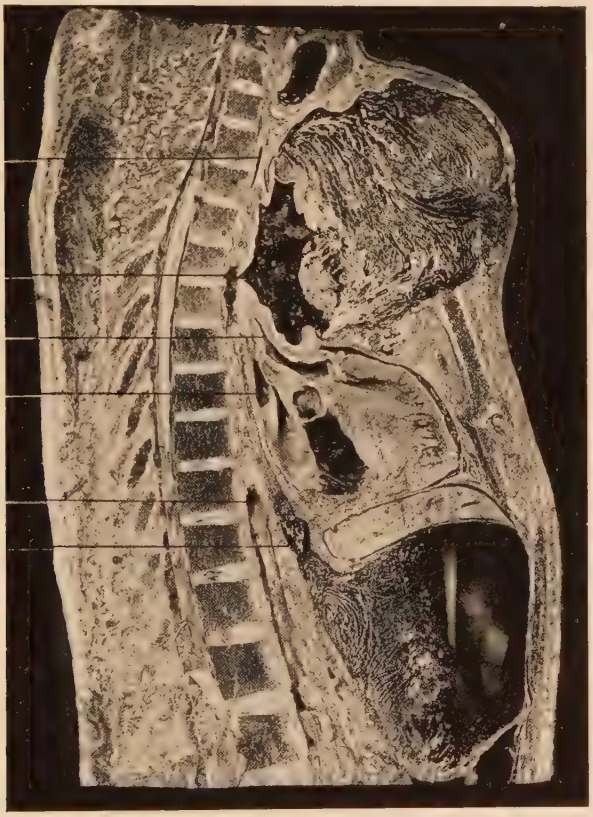

FIG. 7.—*E*, esophagus; *P. A.*, pulmonary artery; *L. A.*, left auricle; *A. V.*, aortic valve; *A. A.*, abdominal aorta; *M. V.*, mitral valve; *C. A.*, coronary artery; *R. V.*, right ventricle; *P. V.*, pulmonary vein; *R.*, rupture into right bronchus.

is only apparent, and is due to the fact that the section was made directly through the interventricular septum.

The pulmonary artery is greatly compressed, and doubtless this factor, combined with the atelectasis of the left lung, accounted in large measure for the extreme degree of dyspnea from which the patient suffered.

The blood clot in the stomach is invariably shown on the posterior surface; this is because the body was frozen in the horizontal dorsal decubitus.

The well-organized laminated clot which fills most of the aneurysmal sac is of interest, since the advisability of "wiring" was at one time dis-

FIG. 8.—*S. V. C.*, superior vena cava; *V. A. M.*, vena azygos major; *R. B.*, right bronchus; *R. P. A.*, right pulmonary artery; *R. A.*, right auricle; *I. V. C.*, inferior vena cava; *K.*, kidney; *P. V.*, portal vein; *Pl.*, pleura; *A.*, aorta; *P.*, pericardium; *S. P.*, in pericardium.

cussed. The pulsation of the aneurysm, which was well marked and expansile, suggested the possible desirability of this procedure, although no wiring was attempted.

With the extreme degree of esophageal compression it seems strange that dysphagia had not been a more prominent symptom. While the

patient had been unable to swallow solid food for some time before his death, liquids gave no great amount of trouble, and certainly the blood which reached the pharynx during the terminal hours passed the stomach without difficulty. The lower portion of the esophagus as well as the stomach contain much clotted blood.

In regard to the site of rupture it is interesting to note the smooth, crater-like character of the aortic intima at this point. There is no tearing here of a thin vascular wall, but what appears to be a giving way of the thick bronchial and aortic tissues at a point where pressure has been most marked and long continued. The aneurysmal intima and the epithelial lining of the bronchus appear as continuous structures at the actual foramen of communication between the aorta and bronchus. It may well be that the force of the blood stream was especially directed against this point.

Fig. 8 shows the gradual decreasing size of the aneurysm, its hour-glass shape previously referred to. The right bronchus is filled with blood but retains an approximately normal shape and position instead of compression and displacement, as noted on the left side. The extent of the aortic dilatation to the right is shown by its presence just anterior to the right bronchus.

A brief summary of our case reads as follows: Patient, a negro stevedore, aged fifty years, who contracted syphilis in 1901, had indigestion, pain and dyspnea twelve years later (1913); noticed a bulging of his chest in 1914, received salvarsan in 1915 and died in 1916.

In every 100 autopsies as they occur in large general hospitals there will be about 3 cases of aneurysm, of which 2 are seated in the thoracic aorta. From 70 to 90 per cent. occur in males. Thoracic aneurysm has been reported at autopsy in an infant of thirteen months, but the majority of cases occur between the fortieth and the fiftieth year of life.

AGE INCIDENCE OF THORACIC ANEURYSM (LEMANN)

Age, years.	Lemann's Touro series.	Lemann's Charity Hospital autopsy series.	Bassett-Smith.	Maximoff.	Maximoff from literature.	Borowsky from literature.	Crisp, quoted by Borowsky.	Emerich, quoted by Borowsky.
1 to 10	..	..	..	..	10	1	1	
10 to 20	..	..	..	..	9	2	5	
20 to 30	1	6	13	4	28	11	71	1
30 to 40	15	17	28	4	71	43	198	7
40 to 50	19	20	6 over	14	100	58	129	16
50 to 60	8	9	..	14	56	46	65	16
60 to 70	3	3	..	5	21	10	25	11
70 to 80	..	..	..	..	5	4	8	5
Over 80	..	1	..	..	4	..	3	2
Unknown	1	10						

As will be noted in the following table, taken from Lemann's[1] article, the most constant physical sign is substernal dulness, while chest pain constitutes the most frequent symptom.

INCIDENCE OF SYMPTOMS: TOURO CLINIC SERIES

	Present in cases.	Absent in cases.	Not mentioned in cases.
Bruit	20	9	18
Tracheal tug	4	16	27
Substernal dulness	33	3	11
Vertebral dulness	15	5	27
Inequality of pupils	4	25	18
Inequality of radials	5	21	21
Unequal sweating	0	0	47
Left recurrent paralysis	6	2	39
Cough	16	5	26
Pain in chest	27	..	20
Pain on pressure over sternum	4	..	43
Pain in right arm	1	..	46
Pain in left arm	7	1	39
Dysphonia	9	1	37
Dysphagia	7	1	39
Diastolic shock	4	14	39
Tumor	6	7	34
Thrill	4	12	31
Pulsation	10	1	36
Wassermann	11	9	27
Tchergunobow modification of Wassermann	10	5	27
Fluoroscope	12	..	35
Roentgenogram	32	1	14
History of syphilis	11	3	33

Practically all aortic aneurysms are a late result of syphilitic aortitis, and about 30 per cent. of all cases of the last-named lesion ultimately develop into aortic aneurysms. The average length of time elapsing between the aortitis and the aneurysm is about sixteen years. The onset of aneurysm may, however, occur within three years or be delayed as long as forty-one years.

The belief currently held that the average length of life after the diagnosis has been established is about two years is borne out by Lemann's figures:

3 months	4 cases
3 to 6 months	12 "
12 to 15 months	17 "
15 to 18 months	10 "
18 to 24 months	14 "
24 to 36 months	10 "
36 to 48 months	8 "
4 to 10 years	9 "

[1] Aneurysm of the Thoracic Aorta: its Incidence, Diagnosis and Prognosis. A Statistical Study, Am. Jour. Med. Sc., 1916, clii, 210.

The following table shows the site of rupture in a series of 603 cases. It will be noted that nearly one-quarter of the cases rupture into the pericardium, the left pleura being the next most frequent location.

RUPTURE (603 CASES)

		Per cent.
Pericardium	150	24.0
Left pleura	101	16.0
Esophagus	53	8.7
Trachea	51	8.4
Right pleura	45	7.4
Left bronchus	38	6.02
Externally	35	5.6
Superior vena cava	31	5.1
Left lung	23	3.08
Pulmonary artery	18	2.09
Mediastinum	11	1.9
Right lung	10	1.6
Right bronchus	8	1.3
Elsewhere (right and left auricles, left ventricles, etc.)	25	4.1

DISCUSSION

Dr. Sailer said it was important to use gold wire and to have a skilled electrician to administer the current, it being unsafe to depend upon a resident, because he will often give too much current at first. One remarkable case had come to the speaker's knowledge of a man whose aneurysm had been filled with a silver wire; later, to his horror and dismay, the *x*-rays portrayed a loop that had reached the apex of the left ventricle. Nothing happened to this man. He displayed no valvular lesion. Six months later the information came that he seemed to be in very good condition. How he had managed to endure a silver wire in his left ventricle, pressing against the valve, was beyond comprehension, but the *x*-rays are still extant.

It is rather remarkable how these patients recover. One man who had an aneurysm of the ascending arch was seen a year later in the lower part of the city of Philadelphia pushing a peddler's cart, heavily laden, over the cobblestones; the man said he was feeling very well and earning a fair living.

Dr. Coplin cited the record of a man who carried a minié ball in his heart for fourteen years and died of something else. A case reported by

the French surgeons of a shot in the heart that was there, could be seen with the fluoroscope, that was anchored in the muscle, anchored freely in an organized position; so there is no reason at all why a foreign body in the heart should not be taken care of.

Dr. Northrup, referring to tolerance of organs to foreign metallic bodies, said there had been a case of a needle in the heart, the needle being in the apex of the left ventricle; the rest of the needle pointed through the mitral valves, transfixing one of them. The child lived that way a year and died; the evidence by *x*-rays was unmistakable. The case came to autopsy. It was remarkable that there was no injury to the needle itself. It was a little black, but not corroded; nothing happened to it, and there were no clots about it.

Dr. Hare (closing) repeated what he had already said, that the technic has to be just right. He emphasized this point because he has been somewhat amused, as well as grieved, to find that there are some who seem to think that they could do this thing because it seemed easy. The last case he knew of justified these remarks. In this particular case the operator told him (speaking ill of the operation) that his milliampèremeter "danced all over the place." All the time he was passing the current his table was in an amphitheater, non-insulated; the surgeon's feet were not insulated and the floor was wet. He used the street current, and the patient suffered from aneurysmal burns. The operator thought it was a very extraordinary thing that the operation had not proved more successful. It was just this error in measuring the current which meant the difference, probably, between success and failure. As a matter of fact the speaker thought it much better, usually, to operate with the ordinary galvanic battery than to use the street current, where there is always the possibility of grounding through some error in technic.

ON THE FOCALITY OF MICROSCOPIC BRAIN LESIONS FOUND IN DEMENTIA PRECOX*

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Abstract

The task of microlocalization.

Work of the topographers.

Problems of a pure functionalism.

Anomalies in dementia precox brains.

Crucial importance of histology of normal-looking brains in dementia precox.

Dissociation of parenchymatous and interstitial lesions in certain cases.

The stratigraphical analysis of the cerebral cortex: supracortex and infracortex.

Many effects of mental dissociation (schizophrenia) probably correlated with supracortical disease.

Correlations of hallucinosis and catatonia with infracortical disease.

Topographical analysis: *a priori* probabilities.

Tendency to lobar and lobular focality of lesions.

Delusions: frontal; catatonic symptoms; parietal; auditory hallucinosis; temporal.

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Exceptional delusions of a fantastic nature probably parietal in origin.

Analysis of four cases.

Summary.

A number of investigators of the mind and its diseases are now pursuing the study of the nervous system along lines roughly summed up in the term microlocalization. But this task must not be conceived narrowly as a task of the histoneurologist or the histoneuropathologist. Microlocalization in the nervous system and especially in the cerebral cortex has threads running to the broadest issues of physiology, embryology, and psychology. Yet no one feels that psychologists, embryologists, physiologists, anatomists or even pathologists in the narrower sense of the term, will solve the problems of microlocalization or even demarcate its problems for solution. When the idea of Flourens that the brain parts were mutually exchangeable in function like so many liver parts, was replaced with the ideas of topographical differentiation which we attach to the work of Hughlings-Jackson and of Hitzig, it was as if the naked eye of observation was replaced with a lens of considerable power. The situation now is that this lens of great power, provided by the work of the embryologists, the physiologists and the clinical anatomists, must be replaced with a lens of still greater power, one that will permit us logically to face problems of microlocalization attaching to physiological complications within the single gyrus. It has become commonplace that the brain is a congeries of organs. It is not so well understood that each gyrus is a wonderland of structures and functions in which rich results are to be expected from hard but fascinating research.

As we look over the history of these developments, we of course find that Bevan Lewis had, in advance of his time, laid down the idea of cell differentiation within the cerebral cortex, clearly distinguishing the large cells of the motor cortex, for example. In much of the work of Meynert and Flechsig, the idea of microlocalization can be discerned. However, even in the embryological considerations of Flechsig, the notion of the gyrus as little more than a functional unit is the prevailing idea. Decades were devoted to the isolation of one neurone after another by ingenious technical

methods and to developing the conception of the nervous system as a mass of embryologically and functionally separate units, expressed for example in the neurone hypothesis of 1891. Listeners to the lectures of Nissl became familiar with his ideas of the structural and functional differentiation of the various cortical parts.

The idea of microlocalization scarcely flourished to the full in the last decade of the nineteenth century, however, since workers were engaged in assimilating the principles of Weigert concerning neuroglia and in trying to find qualitatively the same sort of lesions in the nervous system that they were finding in other organs. In fact, this search nearly culminated in the establishment in the years 1899–1904 of general paresis as a definite example of chronic inflammation of the nervous system. The pathologist was here trying to find, and succeeded in finding, certain lesions scattered in different parts of the nervous system, and lesions of qualitatively the same sort throughout. Nor in the rush of new ideas was the material in general paresis used to the utmost in throwing such light as it might on the problem of microlocalization. Thus, had the world been seriously trying to find out the nature and genesis of mental phenomena and symptoms, it would surely have executed elaborate studies in the distribution of the characteristic paretic exudate, with the idea of correlating these local variations in exudate with processes and symptoms. The issue of such an investigation could only have been positive or negative. As it stands, the situation is doubtful. In fact, it may be confidently doubted whether the paretic exudate itself is at all responsible for many of the characteristic symptoms in paresis, for example, grandiosity, amnesia or even dementia, symptoms which are not found to correspond even roughly with the amounts of exudate discovered in the brains.[1] So far as paresis is concerned, very possibly it was more important to determine it to be syphilitic and to embrace eagerly the opportunities afforded of a Wassermann reaction than to pursue seemingly recondite studies in microlocalization. Meantime the topographical anatomists were laying down the results which the pathologist could at last employ without signal loss of time.

When the interesting and fundamental work of Hammarberg appeared on the histology of feeble-mindedness in 1895, it was plain

that this Swedish investigator had had to spend more than half his time, not on the histopathology of feeble-mindedness, but upon normal histology. The situation is now greatly improved with the work of Elliot Smith who showed that even the naked eye will, under proper conditions, detect striking differences between the gyri of different parts of the brain on section, and especially with the work of Campbell who, after an extensive study of the histology of the different gyri, has offered a valuable atlas with a store of functional comments and speculations.

Even before Campbell, Bolton had laid down exact lines concerning the histology of different parts of the occipital region, and had contributed the idea of visuosensory and visuopsychic regions therein. Similar work has been done by Brodmann in Germany, who, however, feels that functional speculations are hardly in point at the present time. Visitors in the private laboratory of Vogt in Berlin some years since must have been impressed with the tremendous elaboration of structures which could be demonstrated in the different parts of the brain, even by so simple a technical method as the method of Weigert for myelin sheaths. For decades also the world has been watching the development of the ideas of Ramón y Cajal, whose labors stand not second to those of Bolton, Campbell, Brodmann, and the rest of the topographers.

In fact, the research situation is theoretically so promising, in view of the progress along all these lines by workers in different countries, that it is a little surprising that so little neuropathological application has been made of the results attained. There seems to be a curious lack of tempo in neuropathological research. Bevan Lewis's ideas of cortex differentiation came, it would seem, too early to affect the main current of investigation. The work of Donaldson in 1889–90 upon the brain of Laura Bridgman has not been followed up by any considerable series of similar investigations, and the Laura Bridgman work apparently led its author to deeper considerations of growth and development rather than to progress along the line of neuropathology.

Again, throughout the nineteenth century there prevailed the Wundtian psychology. The reader of Wundt's analysis of aphasia, for example, is convinced that, despite the profound distinctions

made, the philosopher was no longer a physiologist and set himself the task of antilocalization in the spirit of a system-maker rather than that of an independent seeker after facts and independent interpretations. The idea of the unity of the mind, a very fine-grained and closely interwoven unity, has prevailed in many quarters, perhaps in all quarters, dominating research. To these psychic unitarians it would have seemed almost a pity if anyone could show, for example, an identity of speech processes with processes of the left inferior frontal gyrus. To the conservative wing of the psychic unitarians was added the force of those strictly scientific persons who feel that a fact is a fact and a speculation is necessarily a bad speculation. Thus, for example, if the simpler ideas of Broca concerning speech localization ought to be modified by the modern concepts of Marie, then this is scored as a victory by those holding to the adamantine unity of the mind on the one hand and by those who are sceptical of all scientific results in the psychic field of whatever sort.

Added to this situation was the Freudian tendency. Disregarding the truth or falsity of the Freudian contentions, it is clear that his followers are engaged much more in finding satisfactory categories of a logical nature in which to place globar tendencies shown by their patients than they are in conceiving the brain functional lines along which an hysterical dissociation might proceed, a repression be mechanized, or a censor be enthroned.

Inasmuch as Descartes made a laughable error in assigning the seat of the soul to the pineal body, it is best for the modern to "play safe" by failing to notice both the pineal body and the brain itself and to solve the problem either by denying that it exists or by failing to consider it at all. One of these modern worthies assured me some years ago that there was no doubt a correlation between mental processes and brain processes and that, theoretically, the "needle" of demonstrable lesions could be found in the "haystack" of neuronic brain systems, but that for his part he regarded that problem as "theoretically" solved and desired to get on with something genuine and practical.

Accordingly, the academic psychologists, if we may so term the Wundtians, and the apparently more radical Freudians, have alike

little interest in the matter of microlocalization, that is, in the correlation of mental with brain processes, either normal or pathological.

It is therefore almost with a feeling of being alone in the wilderness that one endeavors to work in the direction of neuropathological correlation: either there is no problem or it is theoretically settled beforehand. A psychiatrist of light and leading asked me one day what, after all, I was about in working along structural neuropathological lines. Anybody with a logical turn of mind and any capacity for observation ought rather to be busily applying the modern categories of psychopathology to clinical psychiatric and neurological material.

If such doubt of the fundamental value of this kind of work could prevail in the mind of a leading psychiatrist, I felt that I could do no better than bring these general ideas before the Association of American Physicians.

It is as possibly throwing light on the problems of microlocalization that the material in dementia precox struck me as of value. To be sure the world was full of a rather empty discussion as to whether dementia precox was an organic or structural disease. Anyone who professes to find brain changes in dementia precox was perforce regarded as a controversialist, engaged in demolishing the pet ideas of some workers who wanted to show that dementia precox was a disease of maladaptation or a disease with so-called Freudian mechanisms. Let me say therefore that to embark on studies of the brain in dementia precox and to find brain changes therein is not at all to deny that dementia precox is an instance of maladaptation of the individual to his environment and not at all to deny the possible importance of Freudian mechanisms in the disease.[2]

In 1906 I began to study the brain problems of dementia precox and collected first-fruits of that study at the Medical Congresses in 1910[3] and 1913.[4] I then showed that the brains of dementia precox subjects were extremely likely to show evidences of anomaly, that even when there was no anomaly, there were very likely to be microscopic changes. To be specific, I found 23 out of 25 carefully studied brains to be significantly anomalous. I do not mean that the anomalies shown were visible the whole length of the demon-

stration hall, as they are apt to be in brains of the feeble-minded, but I mean that the asymmetries and irregularities were of a demonstrable and photographable nature. Friendly critics offered the suggestion that similar anomalies were to be found in brains of normal persons. Unluckily the brains of normal persons, in large numbers, are not available so far as I know in any laboratory in the world, at least in such a state as to permit proper photographic analysis. However, I think I am able to answer these critics by showing that the brains of subjects of the so-called manic depressive psychosis show such anomalies in very few instances.[5] Using certain criteria, I found four-fifths of my dementia precox brains to show such anomalies and but one-fifth of the manic depressive brains were similarly affected.

But it is one thing for a brain to be anomalous and another for it to be functionally disordered. The underlying hypothesis here is that the anomalous regions of the brain are in some sense weak places therein, such that disease of a toxic or metabolic nature, *e. g.*, at puberty, may unfavorably affect the anomalous and poorly constructed region. These considerations I presented with some histological confirmation at the 1914 meeting of the Association in a paper "On the Direction of Research as to the Analysis of Cortical Stigmata and Focal Lesions in Certain Psychoses."[6] Further reflection on this finding led me to the considerations about tissue decomplication developed at the 1915 meeting.

But it was clear that the few cases of normal-looking brains in dementia precox formed the crux of the situation, since the critics of material from anomalous brains might properly charge the investigator with inability to cull out the acquired from the inborn lesions. I therefore determined to study with sufficient intensiveness the brains of cases of dementia precox that showed no anomalies or scleroses. In connection with this study, five brains were investigated, four of them looking in the general direction of dementia precox and one of them in that of manic depressive psychosis. These five brains were the residuum of a series of 120 coming from psychoses of all sorts.

Before I could bring the topographical problem into clear relief I found that in the analysis of these five brains the problem of

parenchymatous *versus* interstitial lesions stood out. At the 1916 meeting I presented the conception that in the nervous system there should be a dissociation of lesions somewhat similar to that in the kidney.[7] To be sure the parenchymatous and interstitial lesions of the kidney are, as is well known, often if not almost always commingled. But the fact that the lesions in these two types of renal tissue are so commingled in a given case militates not at all against the idea that there are, roughly speaking, two kinds of nephritis—parenchymatous and interstitial. The same theoretical situation holds in the nervous system. I found that parenchymatous and interstitial lesions could be dissociated and combined in the nervous system, much as similar lesions could be dissociated and combined in the kidney. To be sure the parenchyma of the nervous system was a parenchyma composed of neurones and their adnexa and the interstitial tissue of the nervous system was complicated by the fact that a great deal of it is neuroglia tissue, embryologically different from the interstitial tissue of the kidney. Nevertheless, it is well known that many of the properties of neuroglia of ectodermic origin are similar to the properties of mesodermic interstitial tissue. The alterations of the mesodermic interstitial tissue also existent in the nervous system are of far less consequence than those of the neuroglia tissue. The one case of manic depressive psychosis, intensively examined, failed to show convincing degrees of parenchymatous lesion, but the dementia precox cases had well-marked parenchymatous disorder, that is, varying degrees of cell loss, to which the interstitial reaction, that is, gliosis, was found to be not at all proportionate. The result of this study seemed to be that parenchymatous disorder, *e. g.*, cell loss and interstitial disorder, *e. g.*, gliosis, must be investigated separately if we are to make headway in this group of cases. Thus it would be decidedly unwise to argue from the data of neuroglia preparations that the gliosis of such and such an area was an indicator of parenchymatous loss. To be sure the gliosis is probably an indicator of something of general or local significance in the brain. But no facile application of the principle suggested by Weigert's neuroglia work could safely be made. Even if gliosis, as a rule, signifies some degree of wear and tear on the part of the parenchyma of the part affected, yet there was no

good evidence that the gliosis was at all proportionate to the parenchymatous wear and tear.

Having thus shown that the brain conditions roughly corresponded to, *e. g.*, renal conditions and that the histopathological analysis of injured brain tissues must look in both these directions in search of successful correlations, I proceeded to a stratigraphical analysis of the finer cortex changes in these brains, presenting results at a meeting of the American Neurological Association.[8] I tried to study separately the nerve-cell losses on the one hand, and the gliosis (including satellitosis) on the other hand, and then to learn whether the character of these changes in the upper and lower layers of the cortex was of any functional significance. For convenience, I wish to term the upper layers of the cortex supracortical and the lower layers infracortical. In fact, it might be well at times to speak of the supracortex and the infracortex. The comparative anatomists seem to have demonstrated the importance of some such distinction and the literature has for some time contained references to the so-called suprastellate (supragranular) and infrastellate (infragranular) layers of the cortex. Omitting controversial details, it appears that almost all workers are committed to the idea that the majority of the supracortical structures are of more recent evolution than the majority of the infracortical structures. As many of the mental functions in man are of recent evolutionary origin and as all signs point to the cerebral cortex as somehow engaged in these processes, it seems natural to assume that the supracortical layers or what we may term the supracortex is the basis of many of these higher psychic functions. With the same plausibility, we may argue that the infracortical layers or what we may term the infracortex is the basis of such mental or quasimental functions as are found in those animals possessing an infracortex and not yet a supracortex.

All these interpretations are independent of any topographical conceptions and for the purposes of generalization one neglects for the moment the important distinction of the archipallium and neopallium, developed by Elliot Smith.

Taking the whole cortex, by and large, modern work seems to me to invest the supracortex with higher psychic functions than the infracortex.

Now in a disease like dementia precox as psychologically formulated by Bleuler, we find the main feature to lodge in what Bleuler terms schizophrenia. This most valuable term expresses what one might call "split-mindedness" or mental dissociation. Much of modern psychology, whatever may be said to the contrary, is founded on the work of the associationist school of, *e. g.*, John Stuart Mill. We should hardly get on without some of Mill's so-called mental chemistry. Well, for better or worse, associative processes must have their obverse in dissociative processes, and the measure of mental dissociation is the degree of schizophrenia in Bleuler's sense. Kraepelin himself who, on purely clinical grounds of a combination of certain symptoms in certain ways, laid down the conception of dementia precox, has so far admitted the validity of Bleuler's conception of schizophrenia as to use the term schizophrenic very frequently in his description of patients. In one of the most exquisite examples of schizophrenia, viz., the finely divided cleavage of speech known as *Wortverwirrtheit*, Kraepelin has constructed the term *schizophasia* on the analogue of schizophrenia.

We mean then by schizophrenia a process of mental dissociation, a psycholytic or ideolytic process. The cleavage may lie between the intellect and the emotions, such that the emotions do not at all fit the ideas entertained by the patient. Or the cleavage may lie between the emotions and the will, and a bizarre-looking conduct may fit a certain quasinormal state of feeling. But the cleavage is not necessarily so elective and total. The cleavage may be within some particular train of thought. Here is schizophrenia in its best display. Instead of the regular train of thought, we may have a train of thought like a telegraph despatch, or even a train of thought suggesting in its obviously inappropriate sequence a cipher or a set of types reduced to "pi." But absolutely "pied" thinking is not the rule and the so-called word salads are often but passing phases in the development of a dementia precox course.

Here is not the place to expound or to describe schizophrenia. Inasmuch, however, as many of the schizophrenic effects that strike the observer as so bizarre in dementia precox thinking are probably correlated with the operations of the outer layers, that is, of the supracortex itself, you have to inquire whether cases of this order

show lesions preferably in the supracortex. Of my 4 cases of dementia precox, all showed lesions in the supracortex in the nature of cell loss and of more or less disproportionate gliosis, except 1 case. This case was one approximating the so-called paranoia, a disease perhaps allied to dementia precox, but often running years or throughout life without any of the bizarre psycholytic, schizophrenic, thought-splitting phenomena here under discussion. For paranoiacs of this rare description (there may be in a dozen institutions in Massachusetts at this time not more than 25 or 30 of these particular cases) present quasinormal appearances that have been described sometimes as psychic malformations and often give the impression of ability to fit into a reconstructed world with the patients in the center as Kaisers or I. W. W. chiefs therein. In short, many of these paranoiacs, victims of the severest and most intractable psychosis known, are nevertheless without a trace of mental splitting such as I have hinted at above. And in fact the paranoiac in question showed no signs of mental dissociation, but rather showed signs of what might be termed a hypersynthesis of such facts in her environment as fitted her morbid ego and her jealousies. What I am getting at is that the psychopathological analysis of this case of paranoia precisely did not demand any evidence of supracortical disease; in fact, had there been supracortical disease of any moment, we should have wondered whether there had not been some disintegration of the patient's personality, at any rate at the close of her life. It is interesting that this particular paranoiac did show some infrastellate disease which, as will be mentioned below, I regard as correlated with the auditory hallucinations which she showed.

The other 3 cases intensively examined (I may recall that notes were made as to different types of cell loss, gliosis, satellitosis, vascular changes, etc., for each layer in each of twenty-five to thirty areas of the cortex in each subject) showed signs of supracortical disorder as well as of infracortical disorder of varying degrees in different parts of the cortex, and all 3 of these cases showed signs of schizophrenia. This evidence is at least suggestive that supracortical disorder is necessary in schizophrenia. I felt satisfied in my own mind, from the results of the work, that not only is the

cerebral cortex the proper study of the psychologist and the psychiatrist, but that the supracortex is in a still more intimate sense the proper study of the psychologist or psychiatrist who has to deal with the higher functions of what may be called psychic association or synthesis. To my mind, such studies, if in future confirmed, will throw an important added light upon the problems already partly illumined by comparative anatomy.

Let me insist here, if it is not superfluous, upon the fact that I am not proposing an hypothesis to the effect that every time a mental split occurs, a cell drops out of the supracortex. I do not even see in my mind's eye a dendrite dropping off a supracortical cell to signalize the cleavage of an idea. There is very properly much fun to be made of workers who regard ideas as fine transparent substances poured in and out of nerve cells as wine in and out of goblets. Aside from the problem of parallelism and interactionism suggested by the figure that regards brain cells as vehicles for ideas, my own contentions deal rather with the observational facts. I would regard all gliosis as merely indicating and not defining the type of cortical disease in question and I should regard the nerve cell losses or other changes as likewise nothing but indicators of the kind of thing going forward, or perhaps as indicators that something or other is going forward in the injured tissue. To be sure, I would think that destructive brain changes would be more likely to be associated with mental dissociation (with schizophrenia, gliosis) than with other types of synthetic or redistributive mental processes. Supracortical neurone destruction, to put the whole matter in a formula, is to my mind correlated with schizophrenic processes. What, you may well ask, is to be correlated with hypersynthetic, falsely synthetic or redistributive mental processes of the mind twist sort? For the present I, for one, have no idea what cortical process corresponds to these non-destructive, morbid, psychic processes. Mind lack and mind loss *should* correspond with cell lack and cell loss. What we term figuratively mind twist, *e. g.*, false reasoning without loss of sensory intake and power, without loss of memory images, without loss of power of expression, without any evidence of coarse loss of function, remains as a process not readily stateable. Perhaps we must fall back here upon

the idea of physicochemical changes and of anomalous distributions of energy in normal neuronic systems. But these are speculations so remote from observational facts that so far as I can see they cannot even do the observer any harm.

Besides schizophrenia there are other bizarre effects in dementia precox. Perhaps the strangest thing in the world is catalepsy. Catalepsy, catatonia, cerea flexibilitas are not infrequent symptoms in many cases of dementia precox. They all have the character of muscular hypertension somewhat suggestive of hypnotic effects or again of the effects of drugs upon the muscular system. Sometimes the phenomenon of negativism and resistivism reminds one of the Sherringtonian experimental effects showing innervation of antagonistic muscle groups. Possibly these processes are to be explained upon some general line as schizophrenia; possibly they are due to some kind of lysis; some workers are inclined to use the concept of inhibition very freely in the attempt to explain them. They are often a transient phase recurring again after comparatively normal intervals in a schizophrenic patient, and it seems impossible to evoke them by any form of stimulation of the patient.

In a general way, such conditions as catalepsy seem a good deal more like phenomena producible in lower animals than would schizophrenia. Some of the hypnotic or pseudohypnotic appearances in lower animals roughly resemble the catatonic effect. It was in a case of catatonia that Alzheimer first stated that there were nerve-cell changes in dementia precox and it will be remembered that he placed these changes (chiefly gliosis) in the lower layers of the cortex. To a certain extent, my own investigations here confirm those of Alzheimer; at all events, in the cases showing catatonia there were lesions in the infracortex.

Another symptom not at all so bizarre as schizophrenia and catatonia is hallucinosis. Hallucinations are rather quasinormal effects that the normal person rather readily understands and that occur in a great number of mental diseases. Hallucinosis is in short a far less pathognomonic symptom for dementia precox than is either schizophrenia or catatonia. Many forms of hallucination seem to be of so simple a nature that they could well be elicited in the lower animals could we only get at the psychic interiors of

the lower animals to learn their mental contents. *A priori*, therefore, it seemed to me that the disease process underlying hallucinosis ought rather to be in the infracortex than in the supracortex and there was some confirmation of this idea in the cases studied. I mentioned above the fact that late in the disease the paranoiac patient developed auditory hallucinosis. She showed infracortical cell loss of a mild but distinct degree. It will be remembered that the brain of this case was the most nearly normal of all the brains so far studied in the whole series.

The stratigraphical analysis of these brains accordingly proved very alluring. I seemed to get evidence that the supracortex was a region whose disease might well spell schizophrenia, whereas the infracortex was a region whose disease was related with lower level symptoms, such as catatonia and hallucinosis. The supracortex and the infracortex would then be regions of differential interest for the psychiatric investigator, who would seek in the supracortical region for evidences of higher intellectual disorder in the field of association, combination, and abstraction, and in the infracortex for evidences of lower forms of mental disorder, such as catalepsy and hallucinations. I would not stick on the question of higher and lower functions at this point. Catatonia may well be a far more complex matter than many forms of intellectual dissociation; I call it lower because it seems to me that a simpler organism could show catalepsy than disorders of combination and abstraction in the intellectual field.

I have recently reviewed the cell findings in the different cortical areas, assuming that I should find rather suggestive topical correlations between special kinds of symptom and special loci. I assumed that *a priori* no one would be likely to hunt for the source of auditory hallucinations in the smell zone as defined by the comparative anatomists and that one would hardly be likely to look for the basis of visual hallucinations in the superior temporal gyrus!

Perhaps in accordance with the opinion of the learned psychopathologist above mentioned, it is *a priori* certain that in point of fact auditory hallucinations have their basis somewhere in the temporal lobe and visual hallucinations somewhere in the occipital region, and why undertake a superfluous task of setting out exactly

where and under what conditions they occur? We ought to be greatly helped in this matter by the focality of lesions in dementia precox.

In the beginning I had been attracted by the fact that there was often a lobar or lobular hypoplasia, atrophy or sclerosis in these brains. In fact I had tried, reasoning from the gross data alone, to draw tentative conclusions as to the main lines of functional differentiation in the symptoms of dementia precox.

Noting how difficult was the distinction between inborn anomaly and acquired lesion and how uncertain one might be that a given hypoplasia had anything to do with a given disorder of function, I felt that I ought perhaps to investigate cases without gross lesions.

Now one of the most generally significant results of this intensive examination of numerous areas and all layers in dementia precox brains is that there is a certain focality in the microscopic lesions. I still find the focality to be rather a lobar or lobular one than an intragyral focality. To be sure my colleague, Dr. H. I. Gosline, has made some interesting observations upon some exquisitely focal lesions of intragyral distribution, possibly related with tuberculosis, in certain dementia precox brains.[9] Gosline has endeavored to show that the situation of these lesions (demonstrable by fat stains) is such as to fit with my own older contentions as to the relation of certain symptoms to particular regions. Notably Gosline endeavors to confirm my idea of the correlation of catatonia to postcentral lesions. My own work, as here reported, deals not with results of fat stains but with the results of the study of cell losses by the ordinary tinctorial methods for determination of tubercle, at least with nerve cells (Cresyl violet after formalin fixation). I have tried to show the cell losses thus made out as a little more reliable than the fat-stained cells and deposits that Alzheimer, Cotton and Gosline have used. Using the methods of these observers, I obtain too rich a display of lesions, as a rule, to permit correlation.

The kind of focality of lesions which I believe to have demonstrated in these brains is not intragyral, but lobar and lobular, or in certain cases a focality of lesions affecting the whole gyrus. By and large in these brains, as one examines the different layers

within a gyrus, the layers are apt to show throughout the gyrus the same kind of lesions, whether gliosis or cell losses. In short the focality of these lesions is not the focality of tubercles, tumor masses, glanders lesions or exudative lesions. It is rather a focality such that, *e. g.*, the postcentral gyrus on one side is affected in a certain way throughout the gyrus with such and such layers homogeneously affected. The postcentral gyrus of the other side is relatively normal.

What now are the functional results of a study of the topographical distribution of the lesions just mentioned? Can we by focalizing attention on certain gyri discover functional correlations of lesions with certain symptoms?

The functional correlations of my dementia precox studies published in 1910 and 1914–15 were summed up from the topographical point of view as follows:

1. Delusions are, as a rule, based on frontal lobe disease.
2. Catatonic symptoms are, as a rule, based on parietal lobe disease.
3. Auditory hallucinosis is, as a rule, based on temporal lobe disease.

Re the frontal lobe correlation with delusions, I found an exceptional group of delusional cases without frontal emphasis of lesions; but I found a plausible reason for these exceptions. Upon analysis, the non-frontal cases of delusion formation turned out to be cases with a tendency to what may be termed hyperphantasia, that is, to an elaboration of fantasies not more than half-believed, or at any rate not fully believed, by the patient. It is clear that from what we know of the probabilities of localization in the brain, both from a comparative and anatomoclinical point of view, the parietal lobes might plausibly be implicated in the function of imagination and that parietal disease might well be attended with functional disorders of imagination, such as overimagination or what is here termed hyperphantasia.

It is plausible to argue that because the parietal tissue, newly evolved in the higher animals, lying between the tactile postcentral region and the visual occipital region and the auditory temporal region, should be a tissue related with apparatus for combining

these sensory data, a tissue which might unobjectionably be termed a center for combining percepts and concepts involving two or more forms of sensation or perception. Whatever the merits of this *a priori* contention, at all events I found a tempting correlation of fantastic delusions with parietal lobe atrophy.

I summed up the anatomical situation as follows:

"On the whole, the correlation between delusions and focal brain atrophy (or aplasia capped by atrophy?) is very strong, particularly if we distinguish (1) the more frequent form of delusions with frontal-lobe correlations from (2) a less frequent form with parietal-lobe correlations.

"The non-frontal group of delusion-formations, the writer wishes to group provisionally under the term *hyperphantasia*, emphasizing the overimagination or perverted imagination of these cases, the frequent lack of any appropriate conduct disorder in the patients harboring such delusions, and the *a priori* likelihood that these cases should turn out to have posterior-association-center disease rather than disease of the anterior association center. This anatomical correlation is in fact the one observed."

My previous work had also suggested a possible correlation between catatonic phenomena and parietal (including postcentral) disease. Ten of 14 definitely catatonic cases yielded gross lesions in the parietal or other post-Rolandic regions. Of the remaining 4, 2, negative in the gross, proved to be microscopically altered in the parietal region, and there were indications of a correlation in the remaining 2 cases. It must be remembered with respect to correlation that I am using the term "catatonic" here as the name of a symptom. I am not offering a correlation between anatomical or microscopic lesions and the catatonic form of dementia precox.

For example, the symptom *cerea flexibilitas* is not necessarily an indicator that the victim belongs in the so-called catatonic form of dementia precox, despite the fact that *cerea flexibilitas* is one of the prettiest examples of catatonia ever described. Four of the 5 cases in the 1914–15 series that showed *cerea flexibilitas* had parietal anomalies or atrophies and the fifth case, though it was entirely negative in the gross, was a case which showed an extreme

degree of satellitosis in the postcentral region examined microscopically. These observations and certain *a priori* considerations led me to formulate the idea that catatonia, and particularly *cerea flexibilitas* was a form of disorder of kinesthesia.

Re the correlation of auditory hallucinosis with temporal-lobe lesions, it is easy to see that such a correlation ought to exist if any gross correlations at all were expected. In point of fact, 9 of my 12 hallucinating cases have had temporal lobe atrophy or aplasia. One of the 3 remaining cases had ample microscopic changes in the temporal lobes, 1 was clinically somewhat doubtful and, in fine, only 1 of the 12 hallucinating cases could be safely said to have neither gross lesions nor important microscopic lesions in the temporal area.

To sum up then, (1) we expect frontal-lobe lesions in cases of delusion formation, provided that the delusion formation is not of the fantastic and overimaginative sort, whereupon parietal lesions would be expected; (2) we expect parietal lesions associated with catatonic symptoms; and (3) we expect temporal lobe lesions in cases of auditory hallucinosis.

Accordingly, I have collected the microscopic data in the 4 cases at present under discussion under these heads—frontal, parietal and temporal. For convenience I have divided the cortex into three portions—frontal, parieto-occipital and temporosphenoidal. The following table indicates the extent of nerve-cell loss and of neuroglia proliferation, separately in the three regions mentioned:

	I (10.9) 14 years.	II (12.41) 10 years.	III (12.47) 2 years.	IV (11.36) 20 months.
Frontal loci	9	9	9	6
Nerve-cell losses	5	44	35	34
Neuroglia proliferation	7	8	4	3
Parieto-occipital loci	10	9	10	7
Nerve-cell losses	17	47	54	19
Neuroglia proliferation	8	3	2	8
Temporosphenoidal loci	10	10	10	6
Nerve-cell losses	9	48	50	25
Neuroglia proliferation	5	9	1	0

It is clear from inspection of the table that Case I (10.9) stands out as a case in which the parenchymal disease is especially parieto-occipital, since in ten loci, seventeen instances of nerve-cell losses in different layers were found. Here then should be a case with

catatonia unless perchance the lesions in the parieto-occipital area should be exquisitely occipital and not affect kinesthetic areas. In point of fact the lesions enumerated are all in the postcentral, superior and inferior parietal areas and are especially marked in the inferior part of the postcentral gyrus and in the superior parietal region on both sides.

This patient was one that developed characteristic catatonic symptoms, including *cerea flexibilitas* and attitudinizing in the last two years of her life. She also had auditory hallucinosis in those years and showed, as the table indicates, a number of parenchymal losses in the proper area, especially the superior temporal gyrus. Both the parietal and the temporal lesions were largely infracortical in distribution, in accord with the argument mentioned above as to the infracortical origin of catatonia and hallucinosis. It will be noticed from the table that there were comparatively few lesions in the frontal region. The case was one of delusions of jealousy and might have been expected to have shown frontal lesions which, however, were not greatly in evidence. However, upon closer analysis of the delusions, it will be found that they are of a synthetic character and not of a schizophrenic character. They are quasi-normal, and it is not easy to conceive just what histological basis such delusions *ought* to have. At all events none of any consequence were found and the frontal region remains practically destitute of any parenchymal loss and has exceedingly slight evidence of gliosis. Accordingly we may suppose that we are getting histological evidence in this case merely of the terminal hallucinosis and catatonia and not of the essential paranoia of the patient.

If we turn to Case II (12.41) we find a totally different situation. The amount of parenchymal loss, as indicated by the number of loci, is far larger than in Case I (10.9). In fact there are four times as many loci affected, and the lesions are scattered throughout all three regions—frontal, parietal, and temporal. There are relatively more parenchymal losses in the frontal region than in the temporal region and relatively more in the temporal region than in the parietal region.

If we took these data on their face value, we should say that this case ought to be predominantly delusional but also hallucinatory and catatonic.

There was some question whether the patient was not slightly feeble-minded to start with. However, her command of theological verbiage was large and she was always self-supporting up to the time of her psychosis. My point in mentioning this query is that very possibly some of the apparent parenchymal losses are actually due to an initial lack of cells. The interpretation of an initial *lack* of cells in any of these areas would of course look in a different direction from that of an initial *loss* of cells. An initial lack in frontal cells might not at all suggest delusional tendencies; an initial lack of superior temporal cells likewise might have nothing to do with auditory hallucinosis. And a simply constructed parietal mechanism would not necessarily entail disorders of kinesthesia with the production of catatonia.

But taking the parenchymal deficiency as signifying initial *loss*, let us inquire what the symptoms of this case are. Was it predominantly delusional? She showed hallucinations of a doubtful but probably of a hypnagogic visual nature. It is not clear that she ever had auditory hallucinations. The appearance of parenchymal loss has proceeded in all these areas to a marked degree, so marked, in fact, that it is rather surprising that there was no gross evidence of brain atrophy (the brain weighed 1130 gm., possibly a slight reduction from the normal weight; the patient was cardiac and there was such a condition of infiltration of the brain tissue that we can *post hoc* readily believe the brain was slightly and diffusely swollen). In short, the lesions in this brain are so numerous and widespread and so affect both the supracortical and the infracortical regions that correlations of the nature here attempted are impossible. One can find a correlation between almost any symptoms and some properly situated lesion in this case. The patient was deluded, hallucinated and catatonic and had frontal, temporal and parietal lesions.

Let us for the sake of argument, regard the frontal lobe delusion correlation as established; let us regard the parieto-occipital correlation with "feelings of being hypnotized" and the "black cat jumping over a pitcher" as indicators of disease in the parieto-occipital or occipital areas. How then shall we interpret the absence of auditory hallucinations? Without invoking the poverty of

clinical observation and the fact that the patient may have kept auditory hallucinations to herself (she was in point of fact often engaged in vituperative language, some of which may have been of hallucinatory origin or of a responsive nature), we must be interested in the fact that some of the temporal lesions shown are exceedingly heavy and affect both the supracortex and the infracortex. Suppose infracortical, temporal-lobe lesions of a nature suitable to produce hallucinations (we are still ignorant just what sort of lesion ought to produce hallucinations), would it be too speculative to suggest that the existence of severe supracortical lesions might well interfere with the proper combination and abstraction of the infracortical data in such wise as to produce conscious hallucinations? That is to say, the total supra- and infracortical mechanism may be conceived to be so altered that though the conditions for hallucinosis are present in the infracortical zone, the hallucinations are not purveyed through lack of finer connections with the higher psychic apparatus mediated by the supracortical layers. Naturally I do not wish to claim more than speculative value for such considerations. It is along these lines, however, that I feel that much important correlation will be secured in future.

If we inspect the table of local distribution of lesions in Case III (12.47), we find conditions approximating those of Case II (12.41), although the duration of Case III is far less than that of Case II. We find here that the parieto-occipital region has numerous lesions and slightly in excess of lesions, also numerous, in the frontal and temporal areas. The case was a catatonic one, and in fact showed both *cerea flexibilitas* and catatonic stupor and would probably be classified as a case of catatonic dementia precox. It appeared that she had auditory hallucinations which she tried to keep out by covering her head with her arms; but the content of these hallucinations was never made out. An attitude of apprehensiveness, an early phase in which she constantly repeated the words "Father Patterson," "Father Patterson," led us to the idea that she had delusions of persecution or else that she was extremely apprehensive and threw a delusional covering over every-day features of the environment. The most pronounced regions of cell loss were in the infracortical portions of the parietal and temporal regions.

When we come to the analysis of Case IV (11.36) we find that the parieto-occipital lesions are far fewer in number and that the case is more one of losses in the frontal and temporosphenoidal areas. This case, therefore, should show delusions and possibly auditory hallucinations. She never showed convincing catatonic symptoms, although she showed a marked mania and hyperkinesis somewhat suggestive of manic-depressive psychosis. She showed characteristic auditory hallucinosis, and it appears that most of her antisocial acts of a mischievous and silly nature were based upon these hallucinations. That she showed definite delusions, *e. g.*, of persecution or of poisoning, is doubtful. We know little of her history immediately after the onset of mental symptoms which followed confinement in a hospital for consumptives. Throughout here period of observation in a hospital for the insane she showed elation, erotism, mischievousness and silliness somewhat suggestive of manic-depressive psychosis and again somewhat suggestive of the elation of certain paretics. The cell losses in the frontal region were numerous and both supracortical and infracortical in distribution. It is interesting that of all four cases, this one was the case which showed a marked myelin-sheath disorder, a disorder so marked as somewhat to suggest the disappearance of fibers in paresis. The supraradiary fibers were absent in all the frontal regions examined and there was a thinning of fibers in the white matter underneath. In short, the disorder in this case was much more than a fine disorder of minor cell mechanisms and approached the more general and globar disorder of paresis, though of course without exudation. Upon some such lines I would be tempted to try to explain the absence of definite delusions except those based upon hallucinations and irritability. I should be tempted to regard the frontal lobe lesions as of such degree that we might think of the case as one that had lost its frontal inhibitions. At the same time, it must be remembered that no coarse atrophy of the brain had supervened, unless we regard the brain weight—1140 grams—as demonstrating brain atrophy.

SUMMARY. Thanks to the work of Elliot Smith, Bolton, Campbell, Brodmann, Ramón y Cajal and others, the neuropathologist can now afford to attempt finer functional histological correlations

in the field of mental diseases, thus aiding in the problems of microlocalization. The antilocalizing tendencies of the Wundtians and the interest in merely logical categories taken by Freudians should not interfere with progress in microlocalization. Dementia precox, for example, can be called a matter of maladaptation of the patient to his environment or of the patient to himself and also a disease characterized by cortical changes.

Previous work had shown anomalies in a high proportion of dementia precox brains and in a correspondingly low proportion of the brains of manic-depressive subjects. These anomalies may well be interpreted as weak places in these dementia precox brains, and the brains in fact are apt to show scleroses and atrophic processes over and above the anomalies. But certain perfectly normal-looking brains in dementia precox also show the same microscopic changes in lesser degrees than are found in the anomalous sclerotic and atrophic brains. The problem of the present communication has been to work out the focality of these microscopic lesions in a few normal-looking brains studied with unusual intensiveness. In the same series of brains, work of previous seasons had shown a dissociation of parenchymatous (neuronic) and interstitial (neurogliar) changes, indicating a tendency on the part of cortex pathology to resemble the pathology of the kidney. But the majority of brains show mixtures of the parenchymatous (neuronic) and the interstitial (neurogliar) lesions. Recent work in comparative anatomy indicates the rather fundamental importance of distinguishing the functions of the upper cortical layers (what may be called the supracortex) from the functions of the lower cortical layers (what may be called the infracortex). The finer processes of mental dissociation (schizophrenia) *ought* to be correlated with lesions of the supracortex, and such lesions were found in cases with evidence of schizophrenia.

On the other hand, in a case of delusions characterized by no splitting (schizophrenia) whatever, but rather by a process of overelaborate synthesis, there was no evidence of supracortical disorder and, in fact, no proposal can be made for any histological correlation with this process of oversynthesis.

Other processes equally characteristic of dementia precox but

logically far simpler in their make-up, such as auditory hallucinosis and muscular hypertension (catatonia) received suggestive correlation with processes in the lower layers of the temporal and parietal regions respectively.

So far as the tissues of these four cases go, there is little or nothing inconsistent in the findings with the hypothesis that ordinary (non-fantastic) delusions are correlated rather with frontal than with otherwise situated lesions; but the supracortical type of delusions found in certain long-standing paranoiacs whose fine mental processes run in a quasinormal manner, find no special correlation in any region, and the probable lines on which this problem is to be solved remain obscure.

So for auditory hallucinosis, the work seems to afford the expected correlation with temporal lesions. In one case, however, temporal lesions of considerable severity were not attended in life by hallucinations of hearing, but in this case there was also a severe supracortical disease of the temporal region, and it may be that for the production of hallucinations, some congress is necessary between the activation of the supracortex and infracortex respectively.

In previous work on this series the brains had indicated a postcentral and superior parietal correlation for catatonia whose muscular hypertension was accordingly regarded as very possibly a kind of morbid kinesthesia. Present work suggests that the anatomical correlation is not merely to the postcentral and parietal regions but still more specifically to the infracortical parts of these regions.

It may be suggested that the lesions found in samples of tissue in the postcentral, superior parietal, inferior parietal and superior temporal regions indicate a certain systemic tendency in the underlying processes. For these lesions were bilateral and occurred, as it were, in two continuous sheets of tissue on both flanks of the brain in one of the best defined of our cases; these flank lesions were not attended by any similar lesions of the frontal, precentral, occipital and lower temporal and smell regions. The nature of a process which could mildly affect nerve cells and neuroglia on two sides of the brain and also specially affect the infracortical rather than the supracortical portions of these affected sheets of tissue remains a mystery. It is perhaps no greater mystery than that which

attends the distribution of lesions in the spinal cord of pernicious anemia. It remains unsettled whether these lesions are secondary in point of time to a non-cell-destructive phase in the disease, or whether the lesions of which these microscopic effects are indicators began *pari passu* with the symptoms—that is, it remains a question whether we are dealing with the excess wear-and-tear process of cell mechanisms morbidly employed or whether the morbidity of neural function is an exact equivalent of the neuronic and neurogliar morbidity.

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PROGRESSIVE LENTICULAR DEGENERATION ASSOCIATED WITH CIRRHOSIS OF THE LIVER (WILSON'S DISEASE)

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Our excuse for presenting before the Association a case report with its postmortem findings is the rarity of the condition both in America and in Europe. Since Wilson first described the disease in 1912, not more than 26 cases have been reported, of which 13 were observed by various American neurologists. The clinical history of our case was as follows:

Herbert B. White, male, aged twenty-two years, farmer by occupation, referred by Dr. C. M. Wray, of Iowa Falls, and admitted to the medical clinic December 11, 1916.

Entrance Complaints. Painful cramps in the toes of the right foot and edema of both lower extremities.

Family History. Father died at forty-five years of age from tuberculosis of the lungs. Mother is alive and well. Three brothers, two about patient's age and the third five years old, living and well. One brother died in infancy. Two sisters, one sixteen years and the other three years, living and well. The mother denies absolutely any similar trouble in her other children or other members of the family either on the maternal or paternal side. One great aunt died insane. No history of alcoholism, epilepsy, syphilis or other hereditary disease.

Personal History. Patient was born and bred in Iowa and had all his life lived in that State or Kansas or Minnesota. He was a farmer

by occupation and of good habits. He used one cup of coffee a day, but no alcohol. He admitted chewing some tobacco and denied absolutely venereal disease. In childhood he had measles, mumps and whooping-cough, but denied scarlet, typhoid and rheumatic fevers. He was not subject to winter colds, bronchitis, pleurisy or pneumonia. He denied pain, palpitation and shortness of breath. Appetite and digestion were always good. For several years prior to his present illness he had been subject to attacks of diarrhea, lasting for two or three weeks, and usually assigned to some error in diet. The stools never contained blood or mucus. He denied absolutely jaundice, abdominal pain, nausea or vomiting. The urinary system was negative, except for slight nycturia. The patient denied headache, convulsions, nervousness or paralysis previous to the present illness. His brother stated that he had always been bright, intelligent and good-natured, was popular with his friends and of average business ability. He had never appeared emotional and did not worry unnecessarily. The only accident that patient recalled was an injury to the back of his neck five years previously, as the result of a kick from a horse; except that he was unconscious for about fifteen minutes there were no ill effects. For several years before the onset of his present trouble he had been bothered with cramps in the calves of the legs upon first going to bed.

Present Illness. Patient moved to Northwestern Minnesota in June, 1916, where he worked on a farm for a Swedish family. His diet was of a general nature except that meat was not often obtainable. About November 11, following several days of riding on a chain plow, he developed painful cramps in both feet, which were severe enough to cause him to give up his work and return home to Iowa, which he did about November 18. He had no difficulty in getting home, by himself, but immediately upon his arrival his family noted that he was quite emotional and had marked unsteadiness of his gait, as well as tremor of the hands and head, which gradually increased during his three weeks at home. He next noted gradual swelling of the shins, which was at first assigned to a bruise, the result of a kick from a horse while working on the farm in Minnesota. About December 7, 1916, the family first noticed spasms of the hands, particularly when he grasped an object of which it seemed impossible to let go without assistance from some member of the family. On this account he was constantly watched so that he might be relieved of these painful spasms by relaxing the firm grasp of the patient; this procedure always resulted in immediate relief. Shortly after the swelling of the legs appeared there was also noticed some edema of the hands. There had been no fever, no difficulty with the bladder, no dysphagia and no dysarthria. At the onset of the illness the bowels were inclined to be loose, but recently had been quite constipated. The gait had become increasingly difficult and unsteady, so that he had to be accompanied

to the hospital by his brother. His brother was certain that apart from his emotionalism that his character was unaltered and that his memory and reasoning ability were good.

Physical Examination (December 12) by Dr. C. P. Howard. Patient is a sick-looking white male of stated age, with flushed cheeks, groaning with pain, which he refers to legs. This is at times apparently increased in severity, making him cry out for a few seconds. There is no characteristic tetanic position of hands, which are held clinched and often holding the bedclothes. His arms are held almost straight. The thighs are semiflexed at the hips and the legs slightly flexed on the thighs, while the feet are extended to the full. There is no flexion of the toes on the feet He grimaces a great deal and holds his breath for a few seconds during a paroxysm of pain. There is no Chvostek sign. No Trousseau sign. The upper eyelids are decidedly full and suggest edema. The lower lids are also a little puffy; the left hand seems a little puffy but does not pit on pressure. Both legs but particularly the left are edematous and pit on pressure. The skin of the lowers is reddened and rough; over the left shin is an old scab about the size of a bean, which can be readily removed, leaving a granulating surface underneath; there is little or no infiltration. The skin everywhere is harsh and dry, suggesting that of ichthyosis. In addition there is a sudaminal rash over the chest and arms. The hair of scalp, chest and arms is thin and fine; it is unusually scanty over the arms, trunk and legs; there are only a few axillary hairs and a sparse distribution of pubic hair, feminine in type.

The external genitalia are faily well developed; muscles are soft; subcutaneous fat is about normal. Thyroid gland is palpable. Head is well shaped and rather small. The hands are not particularly large; the fingers are long and broad.

Chest is large and symmetrical. Lungs are clear throughout.

Heart: The apex beat is not seen but is just felt in fifth interspace 7 cm. from midsternal line. The heart is not enlarged to percussion. The sounds are distant but regular and free from murmurs.

Pulse, 76, regular, of good force and volume; blood-pressure, 110 mm. systolic and 60 mm. diastolic.

Abdomen is rather distended; walls are held rigidly, but not boardlike; when this rigidity is overcome deep pressure is permitted. Neither liver nor spleen can be felt.

There is no trismus, risus sardonicus; no spasticity between attacks. The neck is freely movable, as are all the muscles at times. The tendon reflexes of both uppers and lowers are normal. The abdominals are present. The plantar is of the flexor type on both sides.

December 11. Hemoglobin, 110 per cent ; red blood cells, 4,410,000; white blood cells, 6600; polynuclear neutrophiles, 62 per cent.; lymphocytes, 28 per cent.; eosinophiles, 8 per cent.; transitionals, 2 per cent.

Blood culture taken; reported negative December 13.

The urine contained a slight trace of albumin, but was negative for sugar, acetone, diacetic acid and microscopically.

December 12. Blood: hemoglobin, 105 per cent.; white blood cells, 5800. Polynuclear neutrophiles, 75 per cent.; lymphocytes, 21 per cent.; eosinophiles, 3 per cent.; transitionals, 1 per cent.

In view of the possibility of tetanus, 5000 units of serum were given intraspinously, 28,000 units intravenously and 8000 subcutaneously today.

Coagulation time of blood eight minutes ten seconds (Brodie-Russel).

Cerebrospinal fluid: 0 cells; Noguchi globulin negative; no increased pressure. Wassermann reported negative December 16.

Serum Wassermann reported negative December 16.

Blood sugar, 0.45 per cent.; blood calcium, 13 per cent.

The carbon dioxide content of the blood was 38 by the Van Slyke method and 27.9 vol. per cent. by the Frederici.

December 13. The boy seems more emotional today and thrashes about like an hysterical case. Mouth dry. Throat red, but with no exudate. Tongue reddened. Edema of upper eyelids persists; that of left hand has disappeared and that of lowers is markedly less; left barely pitting on pressure and right much less. Skin over legs reddened. There is resistance to passive motion of right arm and leg, but none of the left arm and leg. Upon placing one's fingers into his right hand he gradually grasps them firmly and develops a tonic spasm of all the muscles of the extremities, which disappears when the grip is relieved. Trousseau's sign absent after three or four minutes' pressure. Chvostek's sign absent over face and nerves of uppers and lowers. The tendon reflexes are not increased.

Dr. Beifeld reports that, owing to resistance of the patient, the electric irritability tests cannot be carried out with any degree of accuracy. He states, however, that it is not markedly increased.

December 14. General condition much improved. During visit he was free from cramps. The edema of extremities seems much less. The skin shows several lineæ atrophicæ over left leg. The thyroid gland is just palpable and the treachea can be felt with great ease. Trousseau's sign was a little suggestive this morning.

December 15. The stool was brown in color and semisolid. Meyer's test for occult blood was definitely positive. Microscopic examination was negative.

The patient had a better night. He seems brighter. The edema has almost entirely disappeared even from the right leg. The eyelids are less puffy. He has had an occasional nosebleed. There is still some spasm of the lower extremities, with extension of feet; there is also slight flexion of the fingers and wrists. On testing Trousseau the left hand assumes a curious position, more of a claw-hammer than the obstetrical

hand, and there are clonic movements of the fingers with apparently voluntary clonic movements of the arms. No Trousseau on right. No Chvostek on either side.

December 16. Dr. Beifeld reports that the electrical irritability is not increased.

Dr. L. W. Dean noted some exophthalmos, with von Graefe's sign. Fundi negative.

Blood: white blood cells, 7960; polynuclear neutrophiles, 68 per cent.; leukocytes, 29 per cent.; eosinophiles, 2 per cent.; transitionals, 1 per cent.

Following ingestion of 200 grams glucose no sugar appeared in urine in four hours. The carbon dioxide of blood (Frederici) 30 vol. per cent.

December 17. Last night was the best to date except for profuse sweating. Patient cries out every few minutes during visit on account of painful cramps. Denies pain in arms. Claims that cramps are due to the grasping of things with hands, which is an impulse hard to control. Frequently has periods of noisy breathing; no periods of apnea. Eats fairly well. No incontinence of urine or feces. Continues to hold elbow adducted with fingers flexed. Thumb is usually outside of palm. Head is moderately retracted, usually turned to right; no exophthalmos or any of the lid phenomena. Lips slightly cyanotic. Cheeks flushed. No facial paralysis, spasm, tremor or Chvostek. There is more or less constant choreiform movement of the thighs. Legs are fully extended in talipes equinovarus position even in absence of spasms. During painful spells calves are distinctly contracted. The grips measured by the dynamometer are: right, 90; left, 40. He has difficulty in releasing grip; cannot elevate arms above the head, but keeps them in a constant swaying motion. Gross strength of limbs appears normal. The tendon reflexes were all present except both Achilles which could not be elicited. Plantar and abdominal reflexes normal. Sensation intact throughout. Gait interfered with by spasm of the calf muscles, which causes him to walk on toes.

December 17. Hemoglobin, 88 per cent.; white blood cells, 14,080. Differential count: Polynuclear neutrophiles, 73 per cent.; lymphocytes, 23 per cent.; eosinophiles, 4 per cent.

The urine showed a few red blood cells microscopically, but was otherwise negative.

The stomach-tube was passed; no gastric content could be aspirated. On lavage the water returned without any solid material and was blood-stained, but patient was bleeding a little from the nose and gums at times.

December 18. A second attempt for an analysis of test breakfast was a failure, as the stomach was found to be empty at the end of forty minutes.

Today the patient is found bathed in sweat and presenting all the signs of a general infection, with slight tendency to cough and an occasional

nosebleed. If anything the painful cramps have been more frequent recently. Examination reveals a dry, brown tongue. The heart was negative except for a soft, systolic murmur audible at the apex and over the precordia. Spleen could not be felt. There are still tonic spasms of the arms and legs which are now only painful in the hands. On attempting passive motion there is still definite resistance met with in all the muscle groups of the extremities. A second blood culture was taken today and reported negative on December 20.

The skiagram of the sella turcica showed no variation in size or contour from the normal.

December 20. Coagulation time of blood by the Brodie-Russel method was six minutes.

A second lumbar puncture revealed no increase pressure, six cells per cubic millimeter and a negative Noguchi globulin test.

December 20. Patient developed incontinence of urine and stools and became very restless. He vomited on several occasions, and finally at 4 P.M. became comatose. One hour later following a profuse dark emesis he died.

The case was most obscure throughout its course. Tetany seemed excluded, though we thought of pluriglandular insufficiency and kept investigating along these lines. There was nothing to suggest an organic nerve lesion. He always appeared toxic, and toward the end showed evidence of some terminal infection, with suggestive signs of a pneumonia. For three days before his death the temperature varied between 100° and 104° F. Pulse 90 to 120 per minute and the respirations between 30 and 40 per minute.

The autopsy findings came as a great surprise. The cirrhosis of the liver was never even suspected. The liver itself was never palpable, and though the dulness was diminished this was assigned to the moderate tympanites present.

Autopsy December 21 (five hours postmortem), by Dr. C. E. Royce. *Anatomical Diagnosis. Cystic degeneration of the basal ganglia; cirrhosis of the liver, colloid cystic degeneration of the parathyroid glands; bacteriemia; uniform congestion of the lungs.*

The body is that of an adult white male, about 5 feet 11 inches in length, without deformity. The body is well nourished. Rigor mortis is well established. There is no edema present. The posterior surface of the body is livid. The face is also reddish purple in color, and rather blotchy in appearance. The same is true to a lesser degree of the upper part of the thorax. The skin over the elbows, about the umbilicus and over the left shin, is brown and rather scaly. There is a bloody discharge from the nose. On turning the body on the right side a considerable amount of bloody fluid runs from the nostrils. The superficial lymphatics are not enlarged. The pupils are round, regular and equal, measuring $3\frac{1}{2}$ mm. in diameter.

On opening the body the abdominal cavity is found to contain about 350 c.c. of serous, slightly blood-tinged fluid. The liver is seen to be very nodular. The omentum is thick, reddish yellow in color and rather dense. The peritoneal surfaces are nowhere adherent. The intestines are moderately distended with gas. The appendix is embedded posteriorly to the cecum. No fluid is found in the pleural cavities and there are no adhesions. The pericardial cavity contains 50 c.c. of clear yellowish fluid; no adhesions are present.

FIG. 1.—The liver.

Liver. The liver is about the usual size and weighs 1540 gm. and measures 24 x 18 x 8 cm.; its surface is very nodular, the nodules being nearly uniform in size, varying from 5 mm. to 1½ cm. and appearing evenly distributed on all the surfaces. The color of the nodules is a rather light grayish brown and the intervening tissue is brown. The cut surface shows that these nodules are evenly distributed through the substance of the liver and are of about the same size and number as were seen on the surface. The tissue of the nodules is rather friable; the intervening tissue is firm. There is no appearance of umbilication present.

Gall-bladder. The gall-bladder is enlarged and distended. Its surface is a grayish white in color, and only by persistent and severe massage is it possible to express bile into the duodenum. The ducts are found to be patent and without deformity.

Spleen. The spleen weighs 320 gm. and measures 13½ x 7½ x 4 cm. It is bluish in color and somewhat mottled, and the capsule appears

wrinkled. It is bright red on the cut surface and its consistence is moderately firm.

Pancreas. The pancreas weighs 190 gm. and measures 17 x 6 x 2 cm. and presents the usual lobulated appearance. It is grayish red in color and its consistence is uniformly firm throughout.

Esophagus. The esophagus is regular in size and shape and has a smooth appearance on the inner surface.

Stomach. The stomach contains about 50 c.c. of dark bluish fluid and the inner surface shows some erosions and areas of hyperemia.

Scattered through the *small intestine* may be seen patchy areas of bluish color. They measure about 2 x 2 cm., their general shape being square rather than round.

Large Intestine. The large intestine presents on its proximal portion a general grayish-black discoloration of the mucosa, against which the lymphoid follicles appear as lighter colored substance, giving the appearance of trout skin.

Kidneys. The kidneys are slightly larger than usual; the left kidney weighs 220 gm. and measures 12 x 7 x 4 cm., while the right kidney weighs 220 gm. and measures 11 x 7 x 4 cm. The surface of the kidney is smooth and regular. The capsule strips easily. The ratio of the medulla to cortex is as 1 to 2.5. The consistence is uniformly firm.

Adrenal Glands. The adrenal glands are slightly enlarged. The left on section presents an excess of blood in the medulla; the right presents the usual yellow cortex and reddish-brown medulla. The *ureters* are without deformities and are patent.

Bladder. The bladder is smooth and without reddening. The *prostate* seems slightly nodular, but is not enlarged.

Lungs. The lungs are crepitant. They are both dark red throughout and exude a red, frothy fluid on section. Excised pieces float in water. Slightly lighter colored areas may be found scattered through the surface of the lungs, which on section are shown to be superficial. The left lung weighs 480 gm. and measures 22 x 14 x 9 cm.

Heart. The heart weighs 290 gm. and was found filled with vermilion-colored liquid blood. The right border measures 10½ cm.; the left border 11 cm. The thickness of the left ventricle is 2 cm.; the thickness of the right ventricle is ½ cm. The muscle is firm, reddish brown in color and the valves are intact, and without deformity. The intima of the *aorta* and other bloodvessels, as far as they were exposed, was reddish brown in color.

Thyroid Gland. The thyroid gland was rather small, weighed 19 gm., was firm and smooth and in every respect appeared normal.

Parathyroids. The parathyroids were readily found and presented no abnormality.

Testes. The testes were both descended and to the naked eye appeared normal.

Brain. The superficial portion of the brain shows an engorgement of all the bloodvessels and a rather marked excess of cerebrospinal fluid. On manipulation of the brain a reddish fluid is seen to pour from the severed infundibu um. About 2 cm. of fluid was expressed in this way. The dura appeared norma' except for discrete pea-sized areas of opacity on its inner surface.

Pituitary Body. The pituitary body is elongated transversely and weighs 920 mg. It is not especially reddened and its consistence is uniformly firm throughout.

The brain and the upper portion of the cervical cord were placed in formalin for five days and were then examined further.

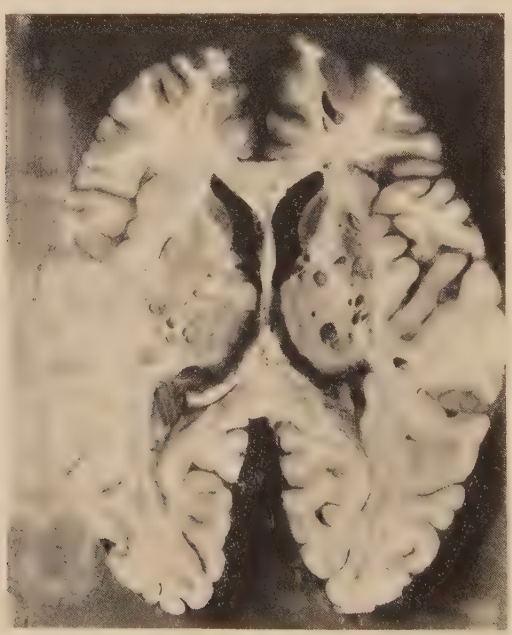

FIG. 2.—The basal ganglia.

The cerebrum divided horizontally by the Pierre Marie coupe d'élection shows in its lenticular nuclei a bilaterally symmetrical cavitation. The cavitation, however, is not sharply confined to the lenticular nucleus but involves, although to a lesser extent, the internal capsule and the optic thalamus. A few sharply circumscribed cavities are also seen in the white matter of the frontal lobes.

The cavities are sharply defined with smooth walls. The shape of each cavity is roughly oval or circular and the longest measurement of any one will not exceed 1 cm. There is slight grayish-red discoloration of the globus pallidus. The putamen seems not to be discolored.

Otherwise the gross section of the brain presents nothing of comment. Neither in gross nor in microscopic preparations was there any pigmentation that would have suggested bile as its origin.

Histological Diagnosis. Progressive degeneration of the neurone and glial elements of the basal ganglia, most extensive in the lenticular nucleus but involving the optic thalamus, caudate nucleus, internal capsule and red nucleus and to a slight extent the white matter just beneath the gray matter of the cortex.

Chronic interstitial hepatitis; lymphoid hyperplasia manifest in spleen and retroperitoneal lymph nodes. Acute congestion of spleen and kidneys. Colloid cystic degeneration of the parathyroid glands.

Histology. Liver. The portions of the liver tissue which appear in the gross specimen as nodules projecting from the surface, on microscopic examination present an approximately normal histological appearance. The intralobular tissue is thickened and infiltrated with leukocytes, many of which are of the polymorphonuclear type. The liver cells of these nodular areas present in some parts large numbers of fat spaces; in others greenish-brown pigment granules may be seen. Congestion in these areas is not a marked feature. The tissue outside the nodules above referred to is composed of laminæ separated by structures which look like bile ducts, and is everywhere infiltrated with red and white blood cells. Endothelial cells and fibroblasts are also numerous in these portions of the tissue. The leukocytes seen are largely of the small mononuclear variety.

Spleen. The capsule of the spleen is thick and the trabeculæ are broad. The finer reticulum of the spleen is increased in density. The pulp contains red blood corpuscles in large numbers. The Malpighian corpuscles have their usual appearance and are somewhat overshadowed by large and denser lymphoid areas, in connection with which no blood-vessels may be found.

Pancreas. The tissue of the pancreas appears to be more compact than usual. With the higher powers the formation of the acini may be seen, but the cells are so crowded together that in most instances the lumen is not visible. The islands of Langerhans are also dense masses of tissue. In general the nuclei are small with the cell body large.

A section from one of the large *lymph* nodes found near the pancreas shows hypertrophy of its constituent parts; the lymph follicles are increased in number. The endothelial linings of the lymph spaces are proliferated and the trabeculæ are more dense than usual.

Kidney. The kidney shows congestion and increase of connective tissue. The tubular epithelium is somewhat granular and the tubules are partly filled with granular débris.

Adrenal Glands. The adrenal glands present their usual appearance, except that there is a little less regularity of arrangement among the

cords. There is diminution in the size of the cells, so that their number appears greatly increased. The cytoplasm of the cells is dense, staining brightly with eosin.

Stomach. The superficial portion of the mucosa is exfoliated. The epithelium of the tubules is in part missing and the remaining cells appear shrunken The lymphoid nodules are numerous and dense. The sections from the *small intestine* show the same loss of epithelium.

Heart Muscle. The cross-striation is visible and presents marked irregularities in that the red and dark bands vary remarkably in their width at the thin portions of some fibers. The nuclei are swollen and present at their poles a few yellowish-brown granules.

Lungs. Most of the air sacs of the lung are filled with red blood cells and with serum. There is no infiltration with leukocytes and the walls of the air sacs are not thickened

Pituitary Gland. The pituitary gland presents its usual glandular structure, without apparent alteration.

Thyroid Gland. The usual histological appearance of the gland is well preserved. The acini are dotted with desquamated epithelial cells in many instances.

Parathyroid. The bloodvessels are distended and engorged with red blood cells. The gland contains many acini, which are filled with colloid and present the same appearance as in the thyroid.

Testicle. Sections from the testicle show the usual histological structure without alteration.

Meninges. Sections from the meninges at the site of the opacities in the gross preparation show simple fibrous thickening of the membrane.

Lenticular Nucleus. Histologically the lenticular nucleus differs from the normal in that the glial tissue is greatly rarefied, appearing as a loose meshwork which is varied in its structural size and density. The cells supported by this meshwork are the nerve cells found here in normal brains plus a few leukocytes, some of which are endothelial and some small mononuclear cells. The distribution of these leukocytes is indefinite. The bloodvessels are thin walled, but contain large numbers of large rod-shaped Gram-positive spore-bearing bacteria.[1] Weigert-Pal preparations of the lenticular nucleus show almost complete absence of myelinated structure in the affected portions.

Optic Thalamus. A section through the optic thalamus including the the border of a cavity shows the cavity to possess no definite lining. The wall, however, is smooth and regular. The tissue adjacent is rarefied by the presence of numerous small cavities which are elongated and tend to a concentric arrangement with the circumference of the large

[1] The presence of the above-mentioned bacilli together with Gram-positive diplococci, also clumps and definite chains of cocci is demonstrable in all tissues examined.

cavity. The nerve cells in this section appear not to be altered. In the walls of some of the bloodvessels may be seen numbers of yellowish pigment granules.

Caudate Nucleus. Histological changes like those of the thalamus are noted, including the yellowish pigment in the walls of some of the vessels.

Internal Capsule. Throughout the entire section imminent disintegration is apparent. Numbers of nerve cells remain intact but numbers are seen which are shadowy. Frequently about these cells the stroma has almost entirely disappeared. No pigmentation is seen in the walls of any of the vessels.

Red Nucleus. Distinct cavities are found here and many more areas where the destruction of tissue has reached a point from which a cavity would have been formed. In these areas of partial destruction the characteristic is numbers of small cavities many of which open one into another and apparently by fusion of these large cavities are formed. Pigmentation is found in the walls of the vessels. As in other portions of the brain tissue where disintegration is in progress nerve cells with shadowy outlines may be seen.

Crus. The sections show an accumulation of leukocytes within the bloodvessels, but otherwise no irregularities. There is no loss of myelinated substance.

Pons. The essential nerve structures and the supporting med'um appear unaltered. The bloodvessels are thin walled, but contain an undue proportion of leukocytes. Some are crowded by endothelial and polymorphonuclear leukocytes. Other vessels are surrounded by a scattering of small mononuclears. There appears to be no loss of myelin sheaths.

Medulla. The medulla presents the same features as the pons.

Cord. There are no histological changes in the upper cervical region which was the only portion of the cord removed for examination.

Cortex Cerebri. The cortex is intact in its essential nervous structure. The pia arachnoid is thickened and slightly infiltrated with endothelial leukocytes and small mononuclear cells.

Cerebellum. No changes are apparent in the cerebellum.

Discussion of the Clinical and Postmortem Findings. Even after leaving the autopsy room we were still completely at a loss for a diagnosis, and it was only after spending some time in looking over the literature that we stumbled across Wilson's paper. It was then perfectly evident that we were dealing with a similar case to that described by Wilson and others. We there-

fore instituted a more careful examination of the brain after it had been hardened in formalin, and were gratified in finding the characteristic changes in the lenticular nuclei, as all of you will see clearly in this specimen which I shall pass around. The brain has been cut according to the Pierre Marie coupe d'élection method. This reveals a bilateral symmetrical cavitation and atrophy of the lenticular nuclei. As you will see even with the naked eye the cavitation is not sharply confined to the lenticular nucleus itself, but involves, although to a lesser degree, the internal capsule and optic thalamus on both sides. There is a slight grayish discoloration of the globus pallidus.

Anyone conversant with Wilson's paper will immediately recognize the strong similarity to those described as acute cases of lenticular degeneration. So far as can be determined by the history of our case, it ran a shorter course than any heretofore reported. So far as the clinical symptoms are concerned there is little to note as peculiar from the other cases. Mentally he was distinctly emotional, but otherwise normal. The peculiar choreiform movement of the extremities, the muscular rigidity and hypertonicity, the painful spasmodic contractions, have all been noted in the cases reported by others. Our case possibly showed more than usual the phenomenon of perseveration, by which we mean a tendency to grasp spasmodically various objects, as the bedclothes, back of a chair and the hands of the examiner, resulting in a painful spasm until disengaged by the nurse or attendant. We were interested in finding this mentioned by Mills, but with this exception, it had not been noted in any other patient but our own. The vasomotor phenomena of redness and edema of the skin were also exceptional and have only been noted previously by Mills. The examination of the reflexes, both superficial and deep, and of the various forms of sensation, as well as the special senses, was as usual entirely negative. While no special tests were made of the hepatic function, none of the usual signs of hepatic insufficiency were manifest. Wilson and all the other writers constantly confess that even when from their former experience they were on the *qui vive* for signs of cirrhosis of the liver, these were conspicuous by their absence during life. Only in an occasional case has

the liver been noted as palpable or decreased on percussion. Very rarely has jaundice been noted.

As regards the postmortem findings, nothing could be more typical than our case, with the exception that the lesion was not absolutely confined to the lenticular nucleus. Wilson in his original description is inclined to emphasize the limitation of the process to the putamen and globus pallidus of the lenticular nucleus and to the caudate nucleus, but as one would naturally suppose additional case reports have shown that the process is not always restricted to the lenticular and caudate nuclei. Ours is not the first in which the optic thalamus, and even the internal capsule and motor cortex, have been involved. In others the pyramidal tracts of the spinal cord have shown slight degeneration. Our case therefore may be grouped with several others in which, though the brunt of the process has been borne by the basal ganglia, other portions of the nervous system have been affected. As regards the cirrhosis of the liver, there is considerable dispute as to whether it is a true cirrhosis or some other form of degeneration, but most are agreed with Wilson that it must be classified as multilobular or mixed cirrhosis.

Any student of neurology will be struck with the close resemblance between the clinical phenomena of Wilson's disease and that of pseudosclerosis as originally described by Westphal and Strümpell. In fact, many are forced to confess that it is impossible to distinguish between the two diseases until a complete macroscopic and microscopic study of the brain and other portions of the nervous system have been made. In reading over the numerous cases described as pseudosclerosis, one is struck rather by the comparative lack of complete examination of the brain and cord than by the absence of definite pathology in the completely examined cases. In fact, I must agree with various recent writers on this subject, who state that the difference between the two diseases seems to be an anatomical one; that is to say, in pseudosclerosis the process is more widespread; in a pure Wilson case more localized. The involvement of the cortex accounts no doubt for the greater alterations in mentality in pseudosclerosis than in the other condition. But as our case illustrates there appear to be all degrees

in the extent of the process from that confined entirely to a portion of the lenticular nucleus to a most widespread degeneration of the central nervous system.

We do not wish to be understood to belittle in any way the accuracy and sharpness of the clinical picture drawn by Wilson, being merely anxious to note the self-evident truth that there is no morbid process, however apparently specific and selective, which restricts itself in its production of clinical and pathological phenomena.

As to the pathogenesis, much has been written. You will all recall, Wilson believes that the degeneration of the lenticular nucleus is due to the selective action of some morbid agent on its cells and fibers and found that this morbid agent was in all probability a toxin associated with a hepatic cirrhosis and possibly generated in connection therewith. He drew the important analogy of the occurrence of so-called "Kernikterus" in certain cases of familial icterus gravis neonatorum, "where in spite of the universal bile-staining of the tissues of the body certain collections only of gray matter in the brain show a marked affinity for the circulating poison while others do not." "The parts that are stained deeply are in particular the nucleus lenticularis and the corpus Luysii (among others), while the optic thalamus, for instance, is scarcely stained at all."

What interested me especially in the literature of pseudosclerosis was a small series of cases which presented among other phenomena an annular yellow pigmentation of the cornea in addition to the cirrhosis of the liver and changes in the nervous system. Further, in three cases either diabetes mellitus or glycosuria or a lowered carbohydrate tolerance was noted. The pigment was thought by some to be silver, by others manganese, while one or two have suggested its close resemblance to that pigment seen in hemochromatosis. We would suggest therefore that in the future study of all cases of cirrhosis, and particularly of those associated with marked pigmentation as is true in hemochromatosis, a more careful examination should be made of the basal ganglia in particular and of the nervous system in general.

DISCUSSION

Dr. Klotz stated that a case similar to that reported by Dr. Howard, with the exception of the age of the patient, had come under his notice. This case has been reported in the literature by Dr. Henrici. Most of the cases of this disease reported by Wilson occurred in children, only one of them being of the age of twenty-four years, and were familial. The case the speaker had under observation was that of a woman, aged fifty-three years with no family history of a similar affection or any nervous conditions, but whose personal history was one of alcoholism. She was a corpulent woman, complaining of general muscular weakness of some weeks' duration. In walking she had a shuffling gait, and she was afraid of falling. There was no jaundice or ascites. Her mind was not clear. She was difficult to understand and occasionally had hallucinations. The movements of her arms were jerky and purposeless. There were no marked tremors. She did not show the characteristic risus spoken of by Wilson. She had considerable dyspnea and cyanosis. Just before death there was some rise in temperature. A Wassermann upon the blood and spinal fluid was negative. At autopsy the important findings were confined to the liver and brain. The liver weighed somewhat over 2000 grams and had the characters of the hypertrophic stage of portal cirrhosis. In the brain a bilateral necrosis of the nucleus lentiformis was found. This necrosis or softening had the appearance of an atrophy of the essential elements of these parts, with a secondary gliosis. The area of degeneration showed a number of small hemorrhages. As an evidence of the degenerative process a condition of diffuse porencephaly was present in the vicinity of the brain lesion. The ganglion cells showed an atrophy and pigmentation.

Wilson classified his cases into the acute and chronic types. This classification was dependent upon the clinical manifestations, and had no relation to the pathological process. In all the cases the liver cirrhosis is in an advanced stage and suggests the elapse of a considerable period of time since the onset. It appears probable that the brain lesions are secondary to the changes in the liver, although there is nothing to indicate the nature of the harmful substance arising within the liver. The brain lesions are not of an inflammatory nature and there is no evidence that bacteria play any part in their development. Although the presence of vacuolations (porencephaly) suggests a similarity with other cerebral conditions in which the bloodvessels are mainly at fault, there is nothing to indicate that in Wilson's disease the vascular lesions are primary.

Dr. Meltzer confessed that until this meeting he had never known what Wilson's disease was, and felt greatly gratified at having heard the paper. He was, personally, especially interested in two points in this case. The patient, on one hand, was suffering from hypercontractility of

his muscles and, on the other hand, the amount of calcium in the blood was definitely increased. He referred to the fact that McCallum and Voegtlin, who found that they can relieve the tetany which follows the removal of the parathyroids by the administration of calcium salts, came to the conclusion that in tetany the calcium content of the blood is diminished and that the presence of calcium in the blood causes a decrease of the hypercontractility. On the other hand, the experiments of Dr. Meltzer and his co-workers point rather to the opposite view, namely, that calcium favors motility. When animals are nearly paralyzed through the administration of magnesium the administration of a calcium salt restores the motility nearly at once. This harmonizes with the observations made by Dr. Howard in his case of Wilson's disease. Dr. Meltzer asked whether the blood was analyzed for its magnesium content, and further, whether he correctly understood Dr. Howard that in this case the thyroid was decreased in size.

Dr. Ramsay Hunt said that Wilson's hypothesis was an important contribution to the physiology of the brain. The lesion in Wilson's disease was exactly circumscribed to the structures of the corpus striatum and therefore has all the importance of an exact experimental lesion limited to this region. As a result of such a lesion there is produced in man a generalized rigidity of the paralysis agitans type—a tremor disturbance which in its essential qualities resembles that of paralysis agitans, and, in addition, a tendency to spontaneous muscular spasms, and sometimes movements of a choreiform or athetoid character.

Wilson in his interpretation of these phenomena was rather inclined to minimize the importance of the muscular spasms and choreiform disturbance. They were not present in his cases, although he admits their presence in the observations of others, notably the cases of Gowers. It is of interest to note that Gowers had originally described the affection under the title of tetanoid chorea, this title emphasizing the importance of the spasmodic and choreiform symptoms.

About a year ago, in a pathological study of a case of juvenile paralysis agitans, the speaker made a careful pathological examination of the central nervous system and found that lesions existed in the corpus striatum and were limited to atrophy of its large motor cells. The smaller cells of the caudate nucleus and the putamen were not affected, and he regarded the juvenile paralysis agitans as a system disease affecting the large motor cells of the corpus striatum.

It is of interest to note that the smaller cells of the corpus striatum undergo extensive degenerations in Hungtington's chorea, while the large motor cells which undergo atrophy in the juvenile type of paralysis agitans are preserved. So it would seem that the disturbances underlying paralysis agitans are referable to the large cell motor system of the corpus striatum and that chorea of the Huntington type is due to a degeneration

of the small-cell system, the large-cell system being motor, and the small-cell system being inhibitory and coördinating in character.

In any massive lesion of the corpus striatum, such as occurs in Wilson's disease, both of these cellular systems would be involved, with the production of paralysis agitans symptoms and also choreiform disturbances; the predominence of either one or the other being dependent upon the degree of involvement of their respective cellular systems.

This conception of the functions of the corpus striatum would explain the variations in the symptomatology of Wilson's disease, some cases showing a predominance of paralysis agitans symptoms and other well-marked features of chorea.

Dr. Rowntree spoke of a family wherein three cases of Wilson's disease occurred, the family having been brought to his attention by a colleague, Dr. Hamilton. The first member was a man, aged twenty-five years, whose disease was typical and who died before reaching thirty, showing the typical changes, including the liver pathology, at autopsy. The second member the speaker had opportunity to observe closely. This man was the most facetious fellow he had ever encountered. He had a very peculiar gait, which would be rather interesting to describe. In the language of the patient, he "looked like a bowl of jelly when walking." When he was walking the flesh of his entire body took on a jelly-like tremor. A peculiar, slow, coarse, tremor appeared in the arms and legs on attempting anything.

One other thing was interesting: The speaker made a series of liver functional studies and no change could be demonstrated in the liver function, at least none appeared in the tests they made. Phenoltetrachlorphthalein appeared in duodenum in seventeen minutes. Fibrinogen, 490 mg. per 100 c.c.; T. n. P. N. of blood, 38 mg.; urea nitrogen, 22 mg. per 100 c.c. Biliary pigments normal. Bilirubin, +; urobilin, 800; urobilinogen, a trace.

It was rather interesting that during observation of this second member of the family, the third, a sister, also came under the observation of Dr. Hamilton, who feels convinced that she is starting the same course.

Dr. Barker declared himself like Dr. Meltzer glad that such a typical case of Wilson's disease had been presented to the Association, the first such so presented, he believed. A study of the history of the subject made him feel that Dr. Howard was quite right in regarding what is called pseudosclerosis and Wilson's disease as identical. There are certain conditions that one sees at autopsy that might be confounded, so far as the naked-eye appearances are concerned, with Wilson's disease. One of these is the so-called "Gruyère-cheese brain;" having seen it once, one will always remember it; the cut brain looks like a slice of Swiss cheese, the appearance being due to the presence of gas cavities, produced by the

gas bacillus, which after death makes these holes in the brain. Another condition that resembles somewhat that seen in the region of the basal nuclei in Dr. Howard's specimen is "lacunar disease" of P. Marie, which occurs in senile persons presenting the symptoms of pseudobulbar paralysis; the patient walks with little steps (*dèmarche à petits pas*). The holes in the brain are very similar to these holes in Dr. Howard's specimen, though in Marie's disease they are probably perivascular cavities.

The relation of this lesion of the lentiform nucleus to the motor symptoms seen during life in Wilson's disease is exceedingly interesting. Through such studies as those of Dr. Howard and those of J. Ramsay Hunt and others of the lesions in paralysis agitans and in Huntington's chorea it would seem that we may hope gradually to acquire a better understanding of the extrapyramidal motor activities and of the functions of the great basal ganglia.

Dr. Kober asked whether in the report of cases there had been any history of exposure either to the inhalation or ingestion of manganese.

Dr. Howard (closing), in reply to Dr. Meltzer's question as to calcium content, said this was the first case, so far as he knew, wherein the calcium content had been studied. They had simply studied the calcium content of the blood because they thought they were dealing with a case of pluriglandular deficiency. In none of the 39 cases which he had carefully read, had the calcium content of the blood been mentioned. A very lucid and interesting discussion of the subject of the lenticular nucleus and its physiological functions would be found among the papers of Dr. Ramsay Hunt. A full description of the physiology and pathology of the lenticular nucleus appears in Kinnier Wilson's original article. Dr. Howard was interested in Dr. Rowntree's statement concerning the one case he had had under observation, in which the liver functional tests were negative, and fully agreed in the matter of the warning uttered by Dr. Barker that we must not interpret holes in the neighborhood of the basal nuclei as being indicative of Wilson's disease. Dr. Howard did not ignore the importance of the aërobic bacteria; but it was their microscopic, as well as their macroscopic, study of the lenticular nucleus which gave them their diagnosis. He had with him a number of the slides should anyone desire to see them.

Answering Dr. Kober's question, so far as the speaker knew no cases of either pseudosclerosis or of Wilson's disease proper had been in any way exposed to manganese; although, as his interlocutor full well knew, there is a symptom-complex in manganese workers, somewhat stimulating the symptom-complex of the lenticular nucleus reported in one or two recent papers. A special study for manganese had been made in a certain group of cases of pseudosclerosis with cirrhosis of the liver and peripheral pigmentation of the cornea; however, manganese could not be demonstrated.

THE NEUTRALIZATION OF ANTIPNEUMOCOCCUS IMMUNE BODIES BY INFECTED EXUDATES AND SERA*

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That sterile filtered inflammatory exudates have the power to modify the course of infection was noted long ago. The chief discussion concerning the nature of this phenomenon has been carried on by Bail and his associates and by those who have contraverted their views. Bail[1] gave to the hypothetical substances existing in pathological exudates, which alter the course of infection, the name "aggressins." He thought that they were secreted by the bacteria during their growth in the animal body and acted by inhibiting or by neutralizing the defensive mechanisms of the body. According to this investigator it is to these substances that the bacteria owe their power to invade the body tissues and therefore it is upon their ability to form them that the property of virulence depends.

Wassermann and Citron[2] have opposed the view of Bail that these so-called aggressins represent substances set free by the bacteria during their struggle against the protective agencies of the body, and believe that they represent merely bacterial substances which may go into solution either within the body or during growth or autolysis *in vitro*, and that these substances act by fixing the humoral immune bodies and so rendering them ineffective; that the mode of action of these substances therefore does not differ from that of dead bacteria. It is not germane to the present discussion to consider the large amount of evidence which has been brought forward to support the contending views, the chief purpose of the present paper being to

* Read before the Association under the title Specific Treatment of Pneumonia.

record the demonstration of large amounts of substances which neutralize immunity principles in the blood and exudates of animals infected with pneumococci, and to indicate the importance of these substances in the specific therapy of acute lobar pneumonia.

The part which these substances play in experimental pneumococcus infections, especially their effect on phagocytosis, has been studied by Hoke,[3] Rosenow,[4] Tschistowich and Jurewich,[5] Zade,[6] and Nunokawa.[7] Tschistowich and Jurewich have made the observation that thoroughly washing virulent, non-phagocytable pneumococci in salt solution is sufficient to render them phagocytable. Rosenow, as well as Tschistowich and Jurewich, has also observed that treating non-virulent, phagocytable pneumococci with the washings from, or extracts of virulent pneumococci is sufficient to render the former non-phagocytable and therefore virulent, and he has found that this property is retained even after washing in salt solution. This writer has given to the hypothetical substances which may be extracted from virulent pneumococci the name "virulin," and Tschistowich and Jurewich have given to the substances which they have obtained by somewhat similar methods the name "antiphagin."

It is evident that these observations, especially those of Rosenow, would render necessary an entirely different conception of the phenomenon from that held by Wassermann and Citron.

In a considerable number of experiments, however, I have been unable to confirm the observations of Rosenow that non-virulent pneumococci may absorb and fix something derived from virulent pneumococci which renders the former virulent, and for the present, therefore, I am inclined to accept the explanation offered by Wassermann and Citron, especially since this conception is sufficient to explain all the following observations.

The first observations on which this communication is based were made on the fluid removed from the chests of persons suffering from empyema. The fluid from these cases was examined for its content in pneumococcus-immune bodies as tested by agglutination and protection. Similar tests of the patient's blood showed that it possessed well-marked protective and agglutinative properties, and we were therefore surprised when we found that the empyema fluid possessed no such powers. A probable explanation seemed to be that, although

the immune bodies were originally present in the exudate they had been observed by the bacteria present, just as they may be from immune blood serum when bacteria are added *in vitro*. It occurred to us, however, to test this empyema fluid after removal of bacteria, to determine whether or not there might be present soluble substances, which would fix or divert the immune substances contained in immune serum. The following is a protocol of one experiment.

Agglutination Tests						
0.4cc Serum I	+	0.4cc empyema fluid			0.1cc Cult. I	2 hrs. 37° - 18 hrs. ice
" " (1:10)		"	"	"	"	++
" " (1:20)		"	"	"	"	++
" " (1:40)		"	"	"	"	+
" " (1:50)		"	"	"	"	−
" " (1:100)		"	"	"	"	−
" " (1:200)		"	"	"	"	−
" " (1:10)		NaCl			"	++
" " (1:20)		"			"	++
" " (1:40)		"			"	++
" " (1:50)		"			"	++
" " (1:100)		"			"	++
" " (1:200)		"			"	++
———		Empyema fluid undiluted			"	−
———		"	"	1:20	"	−
———		"	"	1:40	"	−
———		"	"	1:100	"	−

30 min at 37° C.

TEXT-FIG. 1.—Protocol of an experiment showing the inhibiting action of empyema fluid on the agglutination of pneumococci by immune serum.

CASE I.—E. R., aged nineteen years. Acute lobar pneumonia followed by empyema due to Pneumococcus Type I. 200 c.c. of thick pus were removed at operation. A portion of the fluid was centrifugalized at high speed for thirty minutes, the supernatant fluid was removed to a fresh centrifuge tube and again centrifugalized for one hour, and finally diluted

with an equal quantity of isotonic saline solution and again centrifugalized for thirty minutes. The perfectly clear fluid as examined microscopically contained no organisms.

This fluid was then tested for its power to cause agglutination of Type I pneumococci and also for its power to inhibit the agglutination of pneumococci by Type I immune serum. The results are given in Text-fig. 1.

Protection Tests					
Culture dilution cc.	0.2cc. i.h.s. + 0.2cc. empyema fluid	0.2cc. i.h.s. 0.2cc. n.h.s.	0.2cc. NaCl + 0.2cc. empyema fluid	Culture control	Empyema fluid alone cc.
0.1	D. 20 hrs.	S.	D. 30 hrs.	—	0.5 S.
0.01	" 21 "	"	" 16 "	—	0.3 "
0.001	" 30 "	"	" 38 "	—	0.2 "
0.0001	—	—	" 30 "	—	0.1 "
0.00001	—	—	" 30 "	D. 30 hrs.	
0.0000001	—	—	" 30 "	" 30 "	

TEXT-FIG. 2.—Protocol of an experiment showing the inhibiting action of empyema fluid on the protection of mice by immune serum.

The fluid was then tested for its power to inhibit the protective action of immune serum against infection with Type I pneumococci as tested in mice. To guard against the possibility that the fluid, centrifugalized as noted above, might contain an occasional pneumococcus which might interfere with the result, it was heated for thirty minutes at 56° C. Cultures made from this fluid were sterile.[8] Text-fig. 2 gives the results of this experiment. They show in a striking way that empyema fluids may contain large amounts of soluble substances which inhibit the action of immune serum.

Similar tests have been carried out with a series of these empyema exudates removed by aspiration or at operation. The results have not been so striking in all the cases examined as those shown in the above protocol, though some degree of inhibition has been present in all infected cases. Several sterile serous fluids aspirated from the chest of pneumonia patients, however, have not exhibited this phenomenon. The degree of inhibiting action is apparently dependent upon the degree of infection and the time the infection has lasted before aspiration is performed.

These observations indicate why it is that infections in the partially immunized animal tend to be focal and why, when an animal is infected with organisms of slight virulence, the infection tends to remain localized. It is probable that as soon as bacteria begin to grow in tissue spaces these inhibiting substances appear in the inflammatory exudate, and when the fluid is not readily absorbed the substances accumulate in large amounts, so that finally, as in empyema, it is practically impossible to produce a focal immunity reaction until the focus is opened and the fluid, with its content of neutralizing substance, is removed by drainage, when the bacteria remaining are no longer protected from the natural or artificial defensive mechanisms of the body and so may be overcome. This conception agrees in the main with the view held by Bail and others, though the application of the theory has previously been made rather to the problems of virulence and infection than to those of recovery. The observations previously mentioned also indicate that favorable results can hardly be expected from the treatment of these focal infections with immune serum, either administered intravenously or injected directly into the focus itself unless the pathological exudate has previously been removed. We have made one attempt to treat a patient suffering from empyema by the direct injection of immune serum into the cavity, but without apparent effect. These observations offer the explanation for the failure. In the treatment of focal infections with immune serum, without drainage, it would be necessary to inject sufficient serum to neutralize all the inhibiting substances present, as well as the amount necessary to prevent the harmful activities of the bacteria themselves.

Our next problem was to discover whether or not the inhibiting substances appear in the blood as a result of septicemia. This was first investigated by inoculating rabbits with very large injections of pneumococcus and testing the blood removed during the height of infection for the presence of these substances. To show that this action is due to soluble substances, and not to the bacteria present, the bacteria have been removed from the serum by filtration before testing. The results of one of these experiments are given in the following protocol.

Rabbit 1.—Weight, 1300 gm. July 11, 1916, 12 noon. Inoculated intraperitoneally with 1 c.c. of peritoneal exudate of a rabbit previously infected with Type II pneumococci. 5 P.M. Blood culture shows innumerable numbers of pneumococci.

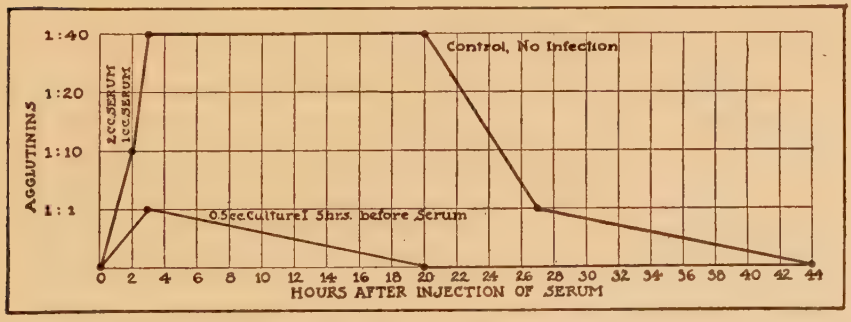
July 12, 10 A.M. Animal very sick. Blood removed by heart puncture. Serum removed from clot and passed through a Berkefeld filter. Culture of filtered blood sterile. The filtered blood was tested for its power to inhibit the agglutinating action of immune horse serum, Type II. The table below shows the results obtained.

Agglutination.		Results after 2 hrs. at 37° C. and 18 hrs. on ice.
0.4 c.c. of immune serum II (1:40) + 0.4 c.c. of filtered serum	After 30 minutes at 37° C. 0.1 c.c. of Culture II was added to each tube	−
0.4 c.c. of immune serum II (1:50) + 0.4 c.c. of filtered serum		−
0.4 c.c. of immune serum II (1:100) + 0.4 c.c. of filtered serum		−
0.4 c.c. of immune serum II (1:200) + 0.4 c.c. of filtered serum		−
0.4 c.c. of immune serum II (1:40) + 0.4 c.c. of salt solution		++
0.4 c.c. of immune serum II (1:50) + 0.4 c.c. of salt solution		++
0.4 c.c. of immune serum II (1:100) + 0.4 c.c. of salt solution		++
0.4 c.c. of immune serum II (1:200) + 0.4 c.c. of salt solution		++
0.4 c.c. of immune serum II (1:400) + 0.4 c.c. of salt solution		+
0.8 c.c. of salt solution		0

The results of this and other similar experiments show that specific inhibiting substances such as those which are present in pathological exudates may also be present in the blood when an animal is suffering from a severe septicemia.

Another method which has been used for testing the presence of inhibiting substances in the blood is the following. A rabbit is infected with pneumococci and after the infection has reached its height immune serum is injected intravenously. At the same time, and as a control, a normal rabbit receives the same amount of immune serum intravenously. Within a few minutes and at varying periods following the injection of the serum, samples of blood are removed from both rabbits and tested for their content in antibodies.

For this purpose agglutination is employed. If no neutralization of antibodies occurs, it is evident that the content of the blood in agglutinins immediately following the injection should be the same as though the immune serum had been diluted *in vitro* with a quantity of fluid equal to the blood contained in the rabbit, and that by making repeated tests a curve showing the disappearance of the immune bodies by destruction or excretion may be constructed. As a matter of fact, numerous observations in normal rabbits have shown that when the rabbit's blood is tested within a few minutes following the injection of immune serum, its content in agglutinins is about that to be expected when the probable volume of blood in the rabbit and the consequent dilution of the immune serum is calculated. On the other hand, when a similar injection is made into an infected animal, the agglutinating power of the serum obtained from it is much less than that calculated from the probable dilution; indeed, agglutinating power may be entirely absent. Moreover, when the agglutinating power is present, though lower than that of the serum of the normal rabbit, and curves are made to show the disappearance of the agglutinating power, it is found that the agglutinins disappear much more rapidly from the serum of the infected rabbit than they do from the serum of the uninfected rabbit. Text-fig. 3 shows in a graphic manner the results obtained in one of these experiments.


1:40
1:20
1:10
1:1
AGGLUTININS
2 cc. SERUM
1 cc. SERUM
Control, No Infection
0.5 cc. Culture 1 Shrs. before Serum
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
HOURS AFTER INJECTION OF SERUM

TEXT-FIG. 3.—Curves showing the agglutinating power of the serum of normal and infected rabbits following the injection of immune horse serum.

In these experiments the possibility cannot be excluded that the fixation or neutralization of antibodies is due to the presence of

bacteria circulating in the rabbit's blood, but previous observations make it improbable that the entire phenomenon can be due to this. It seems probable that the neutralization is due to a considerable extent to the presence of soluble inhibiting substances.

This last method of study is directly applicable to patients, and a study of this kind in patients is of importance, since it is difficult to produce in animals pneumococcus infections which last over a period of a week or longer, such as those which occur in man. Moreover, it was hoped that this study would offer indications for proper dosage of serum and might even be applicable in the treatment of the individual case. In a series of cases, therefore, the serum has been tested for its content in agglutinating antibodies both before and following the administration of immune serum.

The method of procedure was as follows: Samples of the patient's serum were obtained before any immune serum was administered and also five minutes following the first dose. Where more than one dose was administered (and successive doses have usually been given with six- to eight-hour intervals) other samples were obtained immediately before and five minutes following each subsequent dose. Finally, following the last dose, in certain cases, samples were obtained at varying periods to observe the persistence of agglutinins in the blood. The samples from each patient were kept on ice until all had been obtained and they were then tested on the same day and with the same technic for the presence of agglutinins. The agglutination tests were made by the macroscopic method. In each of a series of small test-tubes was placed 0.9 c.c. of the serum, or of the diluted serum. To each of the tubes was then added 0.1 c.c. of an eighteen-hour broth culture of pneumococcus of the type to which the infection was due and corresponding to the serum which had been injected. The results were read by transmitted light after two hours at 37° C., and again after the tubes had remained on ice overnight.

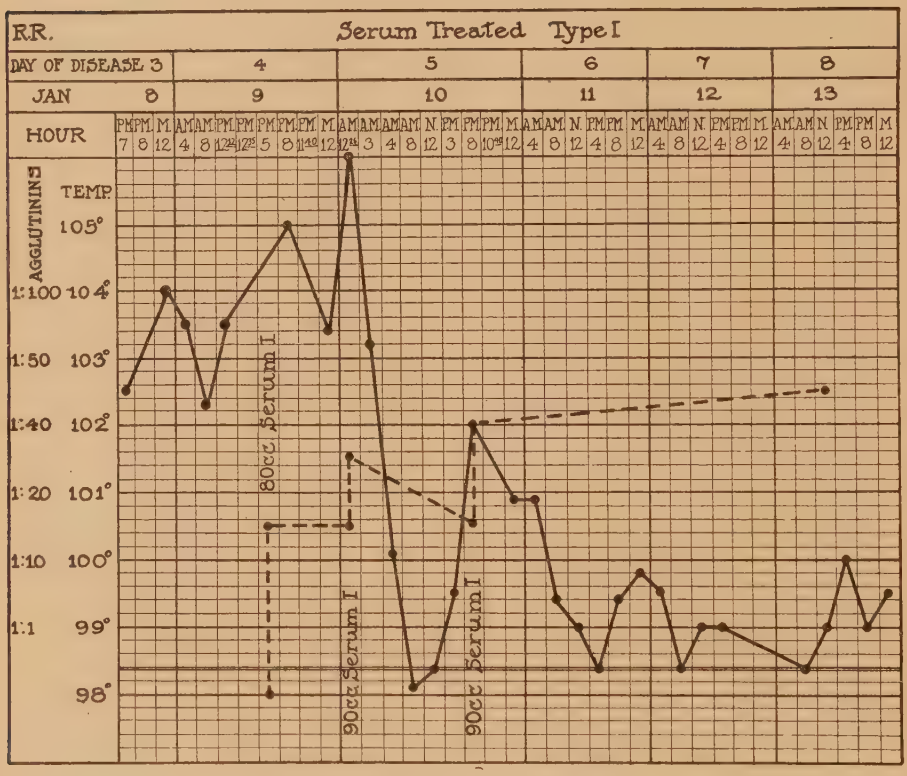
Employing these methods, agglutinin curves have been made from 30 cases suffering from Type I infection and receiving serum, 9 cases suffering from Type II infection, and also serum treated, 7 cases with Type II infection, who received no serum, 4 of Type III, not serum-treated, 2 of Type IV not serum-treated, and 1

case due to Type IV infection who, through a mistake in diagnosis, received several doses of Type I serum, making a total of 53 cases.

Cases Due to Type I Infection Treated with Serum. Of these cases, 3 were treated on the second day, 5 on the third day, 5 on the fourth day, 4 on the fifth day, 9 on the sixth day, 3 on the seventh day, and 1 on the ninth day. All but 2 of the cases recovered. The charts and protocols of several cases, which illustrate the relation of agglutinin titer to the clinical course and to the temperature curve, are given below.

Case I.—R. R., student, aged twenty-two years. This patient was admitted January 8, 1917, at 7 P.M., suffering from pneumonia involving the left lower lobe. The onset had been quite typical with chill, forty-eight hours before admission. He was moderately sick; temperature 102.5° F., pulse 115, respirations 30. The leukocytes numbered 31,000 and the blood culture was positive, the plates showing one colony per c.c. of blood. The sputum was bloody; a small amount was at once inoculated into a mouse. The following morning tests made of the growth in the peritoneal cavity of the mouse showed that the patient was suffering from an infection with Type I pneumococci. 12.17 P.M.: The intravenous injection of antipneumococcus serum was commenced. Although the serum was given slowly, after he had received about 35 c.c. he had some signs of serum intoxication, suffusion of the face, respiratory difficulty, and he vomited several times. The administration of serum was therefore at once discontinued. No tests were made of the agglutinating power of his serum before or after this treatment. The patient's condition did not materially change during the afternoon and at 5 P.M. serum was again administered; this time 80 c.c. were given without any untoward symptoms. A sample of blood was taken just before and another one five minutes following the administration of the serum. When tested later, it was found that the blood before administering the serum contained no agglutinins for pneumococcus; the sample of blood taken following the administration of serum agglutinated Type I pneumococcus in a dilution of 1 : 15. This represents a concentration of antibodies fully equal to that which might be expected, taking into consideration the titer of the serum injected and the probable volume of the patient's blood. The patient's condition did not materially improve after this injection, so that another dose of 90 c.c. of serum was administered at 12 midnight. A specimen of blood which was obtained just before this injection showed that the agglutinating power had not diminished during the time intervening since the preceding dose, and the specimen of blood taken five minutes after the serum was injected showed an increased concentration of agglutinins, so that now agglutination occurred with a

1 : 30 dilution of serum. Immediately following this injection the temperature rose to 106° F. and he had a shaking chill. The temperature then began to fall, being only 98.1° F. at 8 A.M. With this fall in temperature, the patient's condition markedly improved. During the day, the temperature again rose slowly, without, however, any other unfavorable features.

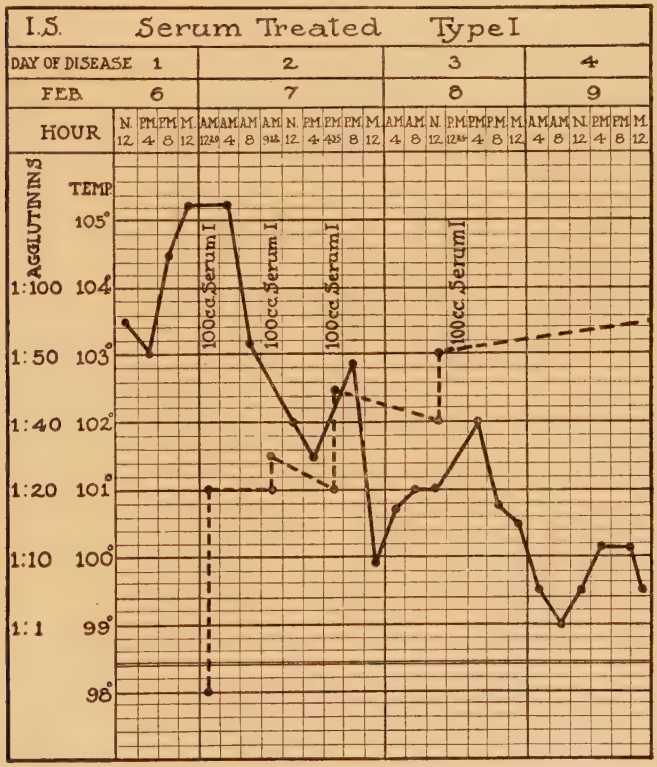


——— Temperature curve.
- - - - - - - Curve of agglutinin titer.

TEXT-FIG. 4.—Chart showing the curve of the agglutinin titer and the temperature curve of R. R.

As the temperature at 8 P.M. was 102° F., it was decided to administer another dose of serum, and 90 c.c. were given, without any reaction. The test of the patient's serum obtained before this treatment showed that the agglutinins had fallen slightly, agglutination occurring in a dilution of 1 : 15, but after the treatment the titer again rose to 1 : 40. Following this treatment the patient made a good recovery.

In this case, therefore, which was mild or of only moderate severity, treated early in the disease, the administration of immune serum was followed by a satisfactory concentration of antibodies in the blood and there was no evidence of fixation or neutralization of the injected immune substances. This is graphically shown in Text-fig. 4.



TEXT-FIG. 5.—Chart showing the curve of the agglutinin titer and the temperature curve of I. S.

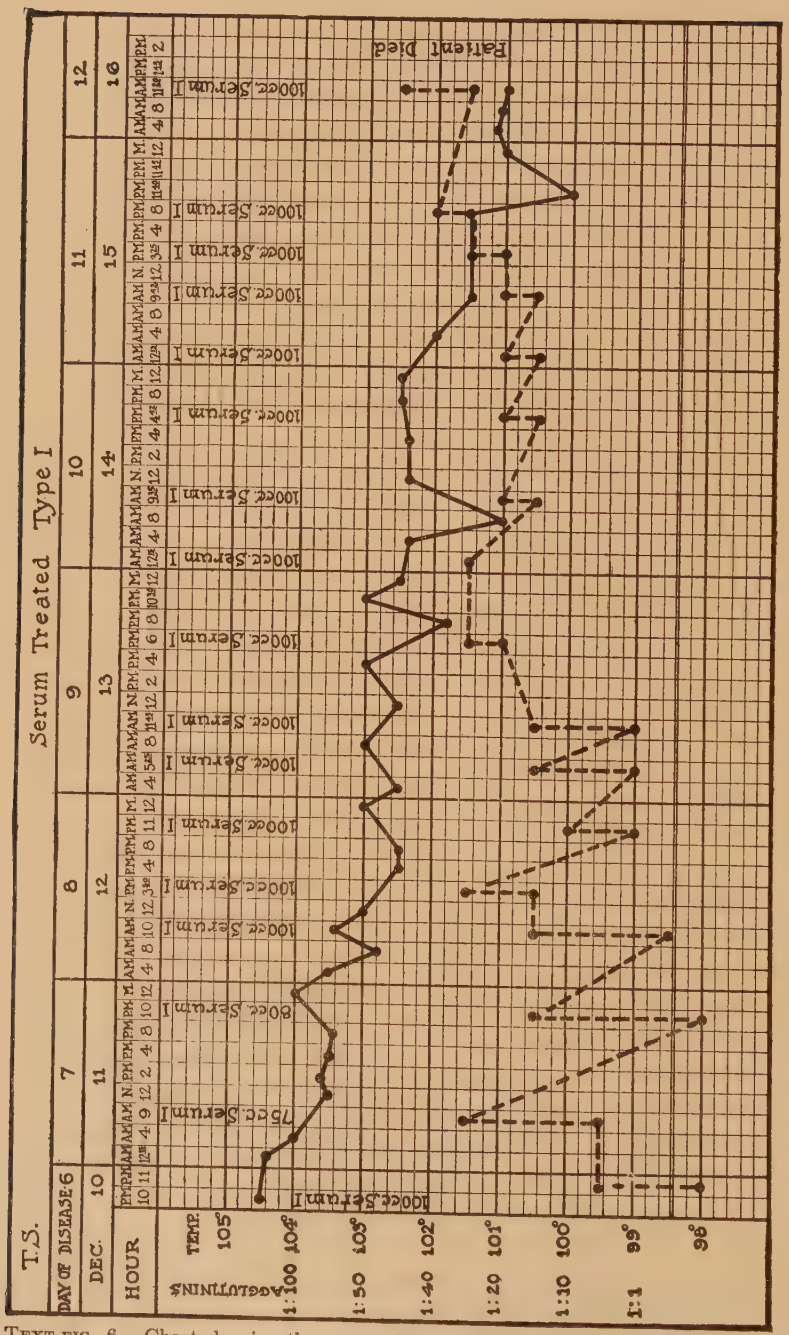
CASE II.—I. S., tailor, aged thirty-two years. This patient was admitted about eight hours following the initial chill. There were definite signs of involvement of both lower lobes and he presented all the characteristic features of acute lobar pneumonia. His temperature on admission was 103.5° F., pulse 120, respirations 48. He appeared seriously sick; the

blood culture taken on admission was positive. The diagnosis of the type of infecting organism was made by inoculation of sputum into a mouse, and at 12 midnight, twelve hours after admission, he was given his first treatment. As the curves presented in Text-fig. 5 show, the first dose of serum imparted to the blood a well-marked power of agglutination, and each subsequent dose was followed by an increase of this property. With the increase of agglutinins in the blood there occurred an improvement in the patient's condition, the temperature fell, and he finally recovered completely.

The two examples given above illustrate the effects of serum treatment in the cases due to Type I infection, when the serum is given early and in large amounts, and when the infection has not reached too high a grade before the treatments are commenced. Since in 28 out of 30 cases recovery followed the administration of the serum, we did not have great opportunity to study cases of this type in which the serum was not effective. In all the cases treated with this type of serum agglutinins could be demonstrated in the patient's blood two to three minutes after the administration of 75 to 100 c.c. of serum. The agglutinating power varied somewhat, though in most cases it occurred with a dilution of 1 : 10 or more. The refinements of the method are not sufficient to justify our calculating in each case the probable dilution and the consequent probable loss in agglutinins in the short interval elapsing before the first tests were made. In general, where the administration of subsequent doses of the serum has not led to a prompt increase of the agglutinins in the blood above the previous level the fall of temperature has been longer delayed and more serum has been required than in the cases in which a regular step-like rise took place. In comparing the temperature and agglutination curves in these cases it has been necessary to keep in mind the fact that the temperature alone does not offer a safe and sure criterion for judging the patient's condition and therefore for the effectiveness of the serum. In view of this fact it has been surprising to see the considerable uniformity with which the temperature and agglutination curves run in opposite directions. With rise of agglutinating power the temperature curve falls.

Of more importance than the immediate rise in agglutinins following the first dose is probably the persistence of the agglutinins in the blood during the subsequent eight to ten hours elapsing before the

following dose of serum is given. In only 5 of the cases did a decrease during this period occur. In 3 of the cases the loss occurred only following the first dose. Following the subsequent doses the concentration reached a high level and persisted. The data in these 3 cases is not sufficient to enable us to state categorically that this loss indicated a greater severity of infection, though taken in connection with our other observations this seems probable. Two of these 3 cases were treated on the fourth day and 1 on the sixth. They required two, three, and four doses of serum respectively and all made good recoveries following the serum treatment. In one of the other cases in which the agglutinating power disappeared before the following dose was given, the concentration of immune bodies following the first three doses was such that agglutination did not occur with dilutions greater than 1 : 5, and following the first two doses this power disappeared completely before the subsequent dose was given. It was only after numerous doses had been given that the concentration of agglutinins reached any considerable level and persisted. Altogether this patient required eleven doses of serum given over seven days. Treatment was commenced in this patient on the second day, but it was not pushed with great vigor at the start, the first dose being 80 c.c., with eighteen hours elapsing before the administration of the second dose of 70 c.c., and twelve hours again elapsing before the administration of the third dose of 80 c.c. This case suggested very strongly the inadvisability of inactive treatment at the start. This patient ultimately recovered and there occurred no extension of the lesion to other lobes, but the temperature remained high for ten days and he was very ill. Finally, the last case in which the agglutinins disappeared between subsequent doses and in which there occurred difficulty in causing a persistent concentration of immune bodies in the patient's blood by the administration of immune serum was one of the two cases which ended fatally. The curves taken from the record of this case are shown in Text-fig. 6. It is apparent from the curves that it was not until treatment had been continued for three days, and nine doses had been given, that a persistent concentration of immune bodies at a high level was attained. Even following this there was a constant tendency for the concentration of immune bodies in the serum to fall, rather than to rise.



TEXT-FIG. 6.—Chart showing the curve of the agglutinin titer and the temperature curve of T. S.

It should be noted that the treatment in this patient was commenced only on the sixth day, and eleven and thirteen hours elapsed between the first and second, and the second and third doses, respectively. He was desperately ill on admission; temperature 104.5° F., pulse 136, and the blood culture showed an extremely high grade of infection, over 300 colonies per c.c. In spite of this he lived until the twelfth day. It seems that in this case the serum prolonged life. The infection and intoxication, however, at the start were so great that, although the infection could be kept down, the intoxication could not be recovered from. In this instance it is likely, judging from the experimental observations, that the presence of large amounts of soluble inhibiting substances in the blood prevented the action of the immune serum. It is probable that in such cases very late in the disease these substances may be so large in amount that no practical amount of immune substances can neutralize them. If these conceptions are correct, the importance of giving very large doses of immune serum at the beginning of treatment is apparent.

In the other fatal case, persistent high concentration of immune bodies in the patient's blood was obtained without difficulty. Nevertheless, the patient's condition did not improve and repeated doses of serum were administered. Type I pneumococci had been obtained from the sputum, and the blood culture showed 47 colonies per c.c. of the same organisms. Treatment was commenced on the sixth day and the patient died on the tenth day. The pathological changes were extensive in both lungs. The autopsy showed a very widespread tuberculous involvement of both upper lobes and the upper portion of the lower lobe on each side. At the base of one lung, however, was a small area of complete consolidation, differing in appearance from the remainder of the tuberculous lung. This proved on study to be a typical acute diffuse pneumonic process and from it Type I pneumococci were cultivated. We have here an instance in which the serum was apparently effective against the specific infection, but death occurred on account of factors associated with the primary and extensive tuberculosis.

A further interesting case in this connection was one due to Type IV infection. Owing to a mistake in the early determination of the type of infection the patient received several doses of Type I serum

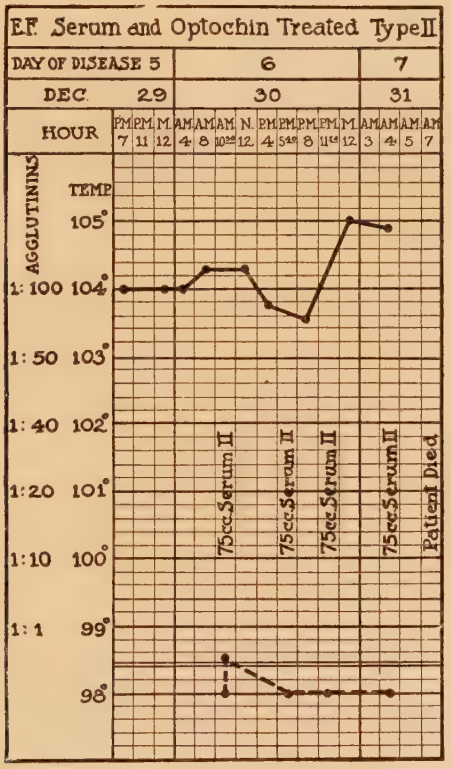
before the mistake was discovered. In this patient, although he was quite ill, the administration of the serum caused a prompt appearance of agglutinins in the blood and this increased with the subsequent doses, without any material fall.

These studies of agglutination curves in the cases of Type I infection, however, while instructive and suggestive, do not after all give definite proof that the effect of immune serum is limited by the presence of soluble substances in the blood. When they are considered, however, in the light of the observations on the Type II cases which follow, the evidence becomes much more suggestive.

Cases Due to Type II Infection. The reader should be reminded at the outset that it has been impossible to produce a serum against Type II pneumococci which is as active either *in vitro* or *in vivo* as is the serum against Type I pneumococcci. Whereas the horse serum against Type I infection is of such a strength that 0.2 c.c. will regularly protect a mouse against 0.1 c.c. of virulent culture, it has been impossible to produce an immune Type II serum of any greater activity than that 0.2 c.c. will protect a mouse against 0.01 c.c. of culture. Moreover, the active Type I sera usually cause agglutination of homologous organisms in dilutions of 1 : 400 or over; the Type II sera usually cause agglutination in dilutions no greater than 1 : 200. It should also be noted that the capsule formation of Type II pneumococci is more highly developed than is that of Type I pneumococci. Dochez and Avery[9] have pointed out that production of precipitable substances in the blood and urine of infected animals apparently bears some relationship to this property of capsule development, the Type III organisms, which possess large capsules, forming most of this substance, the Type II organisms, which have smaller capsules, producing less, and the Type I organisms, which have small capsules, producing still less. While it is not certain that the substances in the infected animals which give rise to fixation of antibodies are identical with those concerned in the precipitation phenomenon, it seems likely that this is the case.

Studies of the agglutinin content of the blood were made in nine cases of Type II infection which received Type II serum. Of these patients, four recovered and five died. Of the patients who recovered, in two treatment was commenced on the third day, in one on the

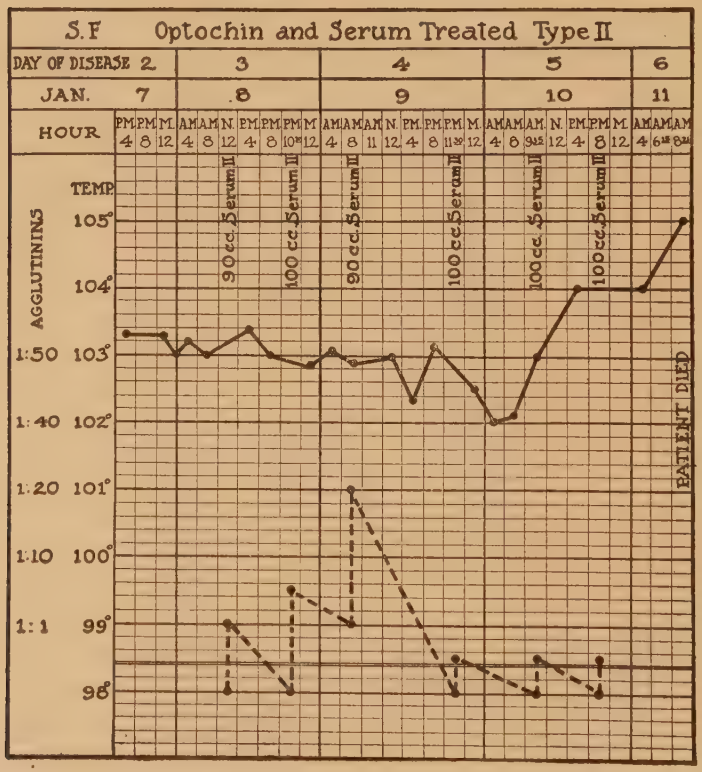
fourth day, and in one on the fifth day. Of the fatal cases, treatment was commenced in one on the third day, in one on the fifth day, and in the others on the sixth day. In all the 4 cases which recovered, a satisfactory and persistent concentration of agglutinins in the blood appeared. In one of the fatal cases, practically no agglutinins



TEXT-FIG. 7.—Chart showing the curve of the agglutinin titer and the temperature curve of E. F.

appeared in the blood in spite of four doses of serum; in one a satisfactory concentration appeared only after three doses, and then disappeared; in another a satisfactory concentration was obtained only on the ninth day, after five doses of serum; in another, while a satisfactory concentration of agglutinins was obtained on the day

treatment was commenced, the sixth day, the patient was at that time suffering from meningitis, from which he died two days later. In the remaining case only one dose of serum was given, two hours before death; no agglutinating power appeared in the blood. Text-figs. 7 and 8 show graphically the results of observations made in two of the fatal cases.



TEXT-FIG. 8.—Chart showing the curve of the agglutinin titer and the temperature curve of S. F.

CASE I.—E. F., porter, aged forty-six years. This patient was admitted on the fifth day of the disease with an extensive lung involvement and very severe septicemia, the blood cultures showing 1000 colonies per c.c. His condition was very serious; temperature 104° F., pulse 104, respirations 64, and, in spite of four doses of serum within twenty-four hours, the

patient died. It will be noted that immediately following the administration of 75 c.c. of serum, the undiluted blood showed power of agglutination, but this property had disappeared within seven hours, and following the subsequent doses the blood showed no agglutinating power whatever. It is evident, therefore, that in this severely infected case the immune bodies in the serum disappeared from the blood as fast as they were administered.

Case II.—S. F., clerk, aged thirty-one years. This patient, though admitted early in the disease, was extremely ill; temperature 103.3° F., pulse 160, respirations 56. The blood culture showed 400 colonies per c.c and the following morning, before the first dose of serum was given, the culture showed 1600 colonies per c.c. Following the first two doses of serum there occurred an immediate appearance of agglutinins in the blood in low dilutions, which, however, disappeared or became minimum in amount before the succeeding doses. In spite of the extreme grade of blood infection, the number of organisms present in the blood diminished following these two doses, the cultures on the morning of the fourth day showing only 20 colonies per c.c. There was a satisfactory increase in agglutinins following the third dose, but it will be noted that fifteen hours were allowed to elapse between this dose and the succeeding one, and during this time the agglutinins had entirely disappeared and the subsequent doses produced little or no effect on the agglutinin content (Text-fig. 8). The patient died on the sixth day.

Five patients suffering from Type II infection who received no serum were also studied to observe the appearance of agglutinins in the blood. All these recovered. In four of these instances at the end of the disease there developed well-marked power of agglutination; in one of them agglutination in the serum obtained on the tenth day occurred in a dilution of 1 : 100. In the fifth no agglutinins appeared in the blood, though this was not studied later than the twelfth day. This patient received optochin, as did, however, several of the cases in which agglutinins developed.

Discussion. Neufeld and Haendel,[10] Dochez,[11] and others have shown that specific immune substances usually appear in the blood during recovery from lobar pneumonia. This is shown by an increase in protective power of the blood for mice against homologous infection. Clough[12] has made similar observations and he and others have also noted that in certain instances the protective power is accompanied by the power of inducing *in vitro* phagocytosis of

virulent homologous pneumococci which are not phagocytable in normal serum. It would seem, therefore, that bacteriotropins represent one form of immune body playing a part in this protective phenomenon. Bull[13] has brought forward experimental evidence which indicates strongly that the phenomenon of agglutination is of great importance in the action of immune serum in pneumococcus infection. It is possible that several different antibodies or phenomena take part in the mechanism of pneumococcus humoral immunity. The observations I have mentioned, as well as unpublished observations made in this laboratory, indicate strongly that natural recovery in pneumonia is associated with the development of humoral immunity and probably occurs because of this development. In the individual case, however, the factors which determine recovery or death cannot be stated so simply. In mild cases probably a very slight grade of humoral immunity may be sufficient to prevent progress of the disease, a grade of immunity which can be detected with difficulty by our present means. In other instances the reaction required on the part of the body may be very great and the immunity phenomena exhibited by the serum when tested outside the body may be very vigorous and marked.

The phenomenon of agglutination offers one ready means for testing the degree of humoral immunity. It is, however, not the only one and it is unsafe to judge of the immunological effectiveness of a serum solely by its agglutinating strength. The protective power and agglutinating power of immune horse serum, however, tend to run parallel. Consequently, the study of agglutinating power of the blood of patients, such as has been made in the present instance, must be of considerable value in indicating the presence or absence of humoral immunity. If recovery in pneumonia is due to the development of humoral immunity, the study of its appearance during recovery and especially of its appearance following treatment with immune serum, should be of significance. In commencing the study it was thought that the method might be employed to graduate the dosage of immune serum in the treatment of the individual case. If recovery is due to the appearance of immune bodies in the blood, the ideal serum treatment would be such that sufficient serum be administered to produce the required concentration of immune

bodies and no more. It soon became apparent, however, that such a method, testing the blood before and after the administration of each dose, involved so much time and labor that it would not be of practical value. It has seemed, however, that the repeated tests of the serum in a series of cases, as has been done here, give us considerable knowledge of the mode of action of the serum and offer valuable suggestions for the routine dosage and mode of application of the serum. The studies have further indicated strongly that during infection not only must sufficient immune substances be added to bring about a concentration sufficient to sensitize all the bacteria, produce their agglutination, opsonification, etc., but in addition there must be a sufficient amount administered to neutralize any soluble substances present in the serum which have the property of neutralizing and fixing the immune substances. It is realized that the occurrence of these soluble, fixing substances in the blood of infected patients has not been directly demonstrated. The experimental observations in animals previously described, however, make it altogether probable that these substances are present in severe infections. It must be admitted that in most instances where there was failure of immune substances to appear in the blood, or where the immune bodies disappeared very rapidly following their administration, bacteriemia was shown to be present before the first dose of serum was administered. In several cases, however, the blood infection could not be demonstrated after the first dose, and nevertheless, rapid disappearance of the immune bodies occurred following the subsequent doses. In one instance in which the rapid disappearance of immune bodies occurred, the blood cultures taken both before and after the administration of serum were sterile. However, it seems likely that in all cases when fixation of immune bodies occurs, blood infection has at some time been present, though the possibility that the fixing substances may, in certain instances, arise entirely in local foci cannot be excluded.

The nature of the substances bringing about the fixation can at present only be conjectured. The demonstration, however, by Dochez and Avery[9] of substances giving rise to precipitates in the blood and urine of infected patients makes it probable that the same substances are responsible for the phenomenon of fixation that we

have studied. They have apparently shown that these substances may be excreted or formed by the bacteria during their growth, and it is also probable that substances contained in the bacteria and set free during their dissolution may give rise to the same phenomenon.

The observations made in this study have a practical bearing on the question of the therapeutic administration of immune serum. The amount of serum necessary to be given does not depend merely on the weight of the patient and therefore on the consequent dilution of the serum in the body. It is also not entirely dependent on the degree of infection present. If the patient is treated early before large amounts of the soluble substance are present, a moderate amount of serum may be sufficient, even though the grade of blood infection may be considerable. On the other hand, if the infection has continued for a considerable time, and large amounts of soluble, fixing substance are present in the blood, the amount of serum required may be very large. It is therefore evident that it is important that the patient be treated as early as possible and before large amounts of these fixing substances are formed. Moreover, the importance of treating very actively at the start in order that all these fixing substances may be at once neutralized and the progress of the infection immediately and entirely overcome is apparent. It is therefore our plan at present to treat all patients with Type I infection with large initial doses, and to repeat the treatment every six to eight hours as long as may be necessary. It is possible that the Type II serum is less effective than Type I serum not only because its concentration of immune bodies is less than that of Type I serum, but also because the power of pneumococci of this type to produce fixing substances is more highly developed than is that of pneumococci of Type I.

Conclusions. 1. In empyema fluids resulting from infection with pneumococci there are present large amounts of soluble substances which have the property of neutralizing pneumococcus antibodies.

2. Similar substances are found in the blood of infected rabbits.

3. When immune serum is injected into infected rabbits the immune substances disappear very quickly, and therefore are prevented from activity in overcoming the infection.

4. When immune serum is administered to patients severely infected with pneumococci, the immune bodies may also disappear very rapidly, and this disappearance is probably associated with the presence of such soluble substances in the blood.

5. The serum only becomes effective when these substances are neutralized.

6. The study of agglutination curves is of value in showing why in certain instances favorable results have not followed the use of immune serum.

7. It is important that in severely infected patients the serum be administered early in the disease and that the initial dosage be large.

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OBSERVATIONS AT THE PETER BENT BRIGHAM HOSPITAL ON CASES OF PNEUMONIA IN RELATION TO TYPES OF PNEUMOCOCCI AND THE SERUM TREATMENT OF TYPE I CASES

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From July 1, 1913, when the medical wards of the Peter Bent Brigham Hospital were opened, until April 15, 1917, 210 patients were recorded with the diagnosis of lobar pneumonia. The individuals thus represented were characteristic of those in the average general hospital in which no particular type of individual dominates, although but few children were admitted. Excluding terminal pneumonias, questionable cases and pneumonias of infants and young children, 23 in all, many of the cases were grouped according to the classification worked out at the Rockefeller Hospital;[1] and we are indebted to that institution for our immune serum. Of the 187 cases considered, 104 were grouped. Such work was done periodically when available men could devote time to it, and some selection of cases was made in that very mild cases, those having crises on admission and cases in children, were frequently neglected, as is manifested below by the mortality statistics of grouped and ungrouped cases. During the past winter all but 2 cases were classified according to their serum reactions. The following statistics were obtained:

	No. of cases.	Per cent.	Survived.	Died.	Mortality, per cent.
Group I* . . .	25	24.0	17	8	32.0
Group II . . .	22	21.2	13	9	40.9
Group III . . .	12	11.6	6	6	50.0
Group IV . . .	45	43.2	34	11	24.4

* Group I cases not treated with serum: 14 cases with 42.8 per cent. mortality.
Group I cases treated with serum: 11 cases with 18.2 per cent. mortality.

The total mortality of the 104 grouped cases was 32.7 per cent., whereas in 83 ungrouped cases this was 16.8 per cent., a combined mortality of 25.7 per cent.

The incidence of cases in the several groups varied moderately from year to year. The notable exceptions were that Group 1 included 61.4 per cent. of the cases in 1914, and that during the past winter 9 Type III cases were encountered, several of which ran unusually mild courses. It has been suggested that sputa obtained in some of the latter instances may have been mouth specimens in which the occurrence of Type III organism is considerable,[2] but only 1 case is subject to such suspicion. Also it is possible that serum now employed in the determination of this group, which was not available in previous years, may detect these cases with greater accuracy.

	Group 1.	Group 2.	Group 3.	Group 4.	Total.
1914	3	3	1	11	18
1915	7	8	0	16	31
1916	7	7	4	10	28
1917 (to April 15)	8	4	7	8	27

Twenty-one positive blood cultures (22.6 per cent.) were obtained from 93 of the grouped cases, of which 15 (71 per cent.) occurred in fatal cases, whereas of the 72 patients with negative cultures, but 14 (18.9 per cent.) died. In 49 unclassified cases, 8 positive blood cultures (16 per cent.) were observed. Two of the patients yielded the Bacillus mucosus capsulatus at autopsy.

No systematic effort was made to employ serum treatment until this past winter when it was administered to all cases with Type I infection. These were treated as soon as the diagnosis was established and large doses were given intravenously, at frequent intervals when necessary. The 11 patients so treated represented both mild and severe infections.

As a rule a critical fall in temperature occurred within a few hours after serum infusion, followed usually by a slight rise which could be controlled by serum. Frequently more than one treatment was necessary to reduce the temperature below 100°. Some cases, usually the more severe ones, showed a precritical rise of 2° or 3°, accompanied by a chill. In these instances, however,

the subsequent fall was proportionately greater, in one instance 8°. Cases in which the disease was of short duration usually required but one treatment.

A cutaneous test, similar to the von Pirquet test, with horse serum protein, was done routinely before treatment, and in 1 instance this was positive, the patient reacting likewise to horse-hair protein. Although $\frac{1}{4}$ c.c. of serum which was then given subcutaneously induced a violent asthmatic attack, by the use of very small desensitizing doses ($\frac{1}{40}$ c.c.), which were gradually increased until intravenous injections could be tolerated, he was eventually made to withstand 70 c.c., and following serum treatment recovered from his pneumonia. A second patient with a history of asthmatic attacks gave a negative skin reaction to serum protein, but had asthma immediately after treatment. He was subsequently found to be sensitive to horse-hair protein.

Serum sickness occurred in most cases about a week after treatment, although it was absent in the 2 asthmatics. This was never very severe, no joint manifestations or prolonged course having occurred. Renal functional tests were not done.

There was but one instance in which serum seemed to have no beneficial effect. This was in the case of a man of fifty-four years, admitted to the hospital late in his pneumonia, in delirium tremens, having intense bacteriemia and a white blood cell count of 4200. He was treated intensively with serum but failed to rally. Another fatal case was that of a woman who responded to serum treatment, but during her apparent convalescence after the temperature had been approximately normal for six days, died suddenly. Autopsy revealed a large thrombus in the right internal iliac vein with an embolus lodged at the bifurcation of the pulmonary artery. She had manifested no signs whatever of phlebitis. A patient with a Type IV infection showed evidences of thrombosis of the right subclavian vein, these being the only examples of this complication in the entire series of pneumonia patients. Two treated cases developed empyema.

The mortality of this treated series was 18.2 per cent. if the case dying of pulmonary embolism during convalescence is included. If this patient is not included as having died as the direct

result of the pneumonia, the mortality was 9.1 per cent. This when contrasted to the 42.8 per cent. death-rate of Type I cases not receiving serum treatment indicates the therapeutic value of anti-pneumococcus serum.

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DISCUSSION

Dr. Janeway stated that Dr. Cole had been good enough to furnish him and his associates with a supply of Type I serum throughout the winter; and while Dr. Bloomfield, Dr. Sydenstricker and Dr. Sutton on his staff had been following the treatment of all their pneumonias and would in detail report their findings, yet, in the absence of Dr. Longcope, slated to lead the discussion, Dr. Janeway thought it might be of interest, because of said staff's slightly divergent experience and the different types of material with which they had to deal, if he should present their figures of 58 cases. They had had, in all, a great preponderance of pneumonia in their colored wards as against the white, which is the usual experience in Baltimore. Against the usual experience, however, the fact that the mortality had been one-quarter among the colored, and one-third among the white, a definitely lower mortality in the colored patients than in the white.

In their treated Type I cases, although the series was not yet complete, they had records of 20, there was a very definite apparent evidence in favor of the reduction of mortality by the serum. On the other hand, he thought it quite fair to say that among the untreated cases were those moribund on admission to the hospital, dying anywhere from four to twelve hours after admission. They had had only 4 Type I cases in the white wards, with a 50 per cent. mortality; 1 of said cases having been extremely protracted, and dying in the end of a terminal overwhelming septicemia, with suppurative meningitis. For the most part, both in their fatal treated cases and their fatal untreated cases, termination has been by suppurative meningitis, or suppurative arthritis, with an overwhelming septicemia. During the entire winter they had no case of empyema, and none of suppurative pericarditis.

The figures for Type II are rather interesting, as showing a relatively low mortality in the colored wards; out of 15 such pneumonias during the

winter only 4 deaths occurring, a death-rate of only a little over 25 per cent.; whereas in the white wards, there having been 2 pneumonias, 1 fatal. This year, as compared with last, they had had only 1 Type III case, and that case recovered. The Group 4 pneumonias, again, had been unusually fatal in the white wards; while in the colored wards a very low mortality had been experienced. Besides these they had also had one Friedländer's bacillus pneumonia, with a gangrenous abscess of the lungs, of course fatal. There had been made daily by Dr. Sydenstricker and Dr. Sutton, blood cultures on all treated cases and on a number of untreated cases; and the one outstanding fact in the serum treatment was the readiness with which the blood could be rendered sterile after the administration of the serum. That had been conspicuous throughout, and seemed to him one of the most important evidences of the efficacy of the serum from a purely objective stand-point; because it had been quite clear, with many of these cases coming in with a large number of colonies in the blood, that the course would have been an extremely rapid one to a necessarily fatal termination. He thought, that of these cases of theirs dying in the end, a number had had their course very materially prolonged by the use of serum. It is quite possible that we shall learn how to handle these cases, perhaps, so as to not only prolong, but eventually to save life; or how, with the combination of optochin and the serum, that will be possible. One was a white man with an intense delirium and behaving as bad alcoholics used to. The blood was kept sterile for nearly two weeks. The patient simply emaciated, so that it seemed possible that he was developing a miliary tuberculosis. In the end, however, he developed a suppurative arthritis, and a final overwhelming terminal sepsis.

The agglutinins had disappeared from the blood as rapidly as Dr. Cole had reported; in some of their worst cases, particularly one man to whom they gave a total dosage of 1300 c.c., they disappeared completely from the blood within twenty-four hours after the administration of 100 c.c. of this serum. Of all their cases that particular man's was the most remarkable. His illness ran throughout a period of considerably more than a month; and he developed a serum sickness with the most extreme generalized lymph-node swelling the speaker had ever seen; so much so, that they had thought he was developing abscess of the neck; all of it finally subsiding, and apparently associated with this serum sickness. They had not seen any critical terminations in the serum-treated cases and had seen little effect on the temperature chart which they could attribute to the administration of serum. They had seen no reduction in the duration of the disease, but rather a lengthening; and a most remarkable experience had been that in many of these cases where they had given repeated large doses of the serum, as stated, 1300 c.c. in the one case and 800 or 900 c.c. in another, the serum sickness had appeared before the defervescence from the pneumonia; it had been impossible to set any date for the onset of

the serum sickness; there had been instead, a gradually progressive serum sickness, stretching itself out sometimes over two weeks, and sometimes with a relapse or two, after the original attack, usually the joint pains first, the urticaria coming out about the time for the ordinary serum sickness to appear. The serum pyrexia merged with the slow lysis of the pneumonia; so that the febrile curve of many of these patients had been a full month and delayed resolution had been extremely common. They had watched numbers of cases over long periods; and both *x*-ray and physical signs proved delayed resolution.

An interesting fact had been that the usual pneumonia this winter was of an extraordinarily protracted course, with defervescence by lysis; and that had been more true of the serum-treated cases than of those not so treated. They had received a few cases in less than five days from the onset of the disease, and their behavior had been practically the same.

He wished to say a few words about the reactions. They had been quite impressed with what Dr. Cole had called attention to, namely, the lack of favorable effect from non-specific reactions. They had had several alarming to see, and to him it was quite clear that that effect of the serum cannot be attributed to the production of the non-specific symptoms of intoxication of the patient, but is entirely different from such effects, as Dr. Miller procures in his cases of arthritis treated with typhoid vaccine. The reactions had seemed to have a very definite relation to the quantity of serum administered. They had not had any severe reactions with less than 75 c.c. of serum administered at one time. They had had 1 case who responded severely on two successive occasions to serum beyond 75 c.c., even though given exactly in accordance with the rules Dr. Cole has laid down.

Dr. Janeway could not say that any great harm had resulted, except that in 2 cases it had caused great suffering to the patient himself, the joint pains having been distressing. The prolongation of the temperature, and the lack of certainty as to whether they were dealing with serum sickness or a complication of pneumonia, particularly an empyema, was trying.

Dr. Meltzer asked Dr. Cole whether the antagonism of the substance, discovered to be present in empyema, is specific against the antiserum of Type I. He asked further whether the action of the antiserum upon isolated hearts had been studied; the serum may occasionally perhaps affect unfavorably the contractility of the heart. Dr. Meltzer remarked that no doubt the successful action of the antitoxins depends greatly upon the degree of the virulence of the causative microörganism. Even in diphtheria the antitoxin treatment proved to be very little effective in epidemics in which the Klebs-Loeffler bacillus was found to be very virulent. The virulence of pathogenic organisms varies in various years.

Are there facts to show that it may vary in the same year and at the same season according to localities? Are there, for instance, facts which could throw light upon the question whether the virulence of Type I pneumococcus has been different, or the same, in all cities where such studies were made?

Dr. Litchfield said he could bear testimony as to the efficacy of the serum.

Dr. Cole (closing) said that the serum apparently acts by overcoming the infection, and no specific effect on the circulation apart from the general effect has been noted. Variation in the virulence of pneumonia at different times and places is very difficult to accurately determine. To judge merely by impressions is very likely to lead to error. One of my assistants who had had considerable experience in Edinburgh once said to me that he had not seen in Edinburgh the type of pneumonia we have in New York; it is so much more virulent here. Within a few weeks Dr. Gibson published statistics for a considerable period of years from the Royal Infirmary in Edinburgh, and the mortality was about the same as that of the hospitals in New York. The mortality in the good large hospitals of all the cities in this country is about the same.

The question of meningitis in pneumonia is an extremely interesting one when considered in the light of the work which Dr. Bull did on the serum treatment of experimental infections of rabbits. If the injection of serum was delayed too long or was not of sufficient amount, those animals develop meningitis. The observations which have been presented today seem to show why when treatment is not sufficiently active to bring about complete cure, complications such as meningitis may occur, and why, when such complications are already present, it may be very difficult or even impossible to bring about a cure. So also in some of the very severely infected cases late in the disease, it may be impossible, for the reasons we have mentioned, to inject sufficient serum to overcome the infection. As we all know, even in diphtheria, if the administration of vaccine is too long delayed, no amount of antitoxin will be efficacious.

VENTRICULAR FIBRILLATION IN MAN, WITH CARDIAC RECOVERY

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The interest in ventricular fibrillation as a disturbance of the cardiac activity of man has been centered about the role this phenomenon may play in causing sudden death. It has been generally accepted that when the human ventricles pass into a state of fibrillation, death is an almost immediate and an invariable consequence.

Ventricular fibrillation can be determined definitely by electrocardiograms, as its presence is indicated by a well-defined type of record. This type has been frequently obtained from animals in which ventricular fibrillation was directly observed in the exposed heart. The usual waves that are produced by the passage of the excitation impulse through the ventricles and the resulting contraction disappear, and in their place rapidly recurring more or less irregular waves occur, following each other so closely that no period of cardiac inactivity is indicated. The waves vary in height and in form, and short stretches of diminished size are apt to occur at intervals in the records.

Although ventricular fibrillation may be a frequent cause of sudden death of man, very few electrocardiographic records have been obtained which signify its presence, because it is necessarily transient, as it is in most instances incompatible with life. Records obtained by one of us[1] from 7 cases at the time of death from

various causes indicated that fibrillation of the ventricles preceded briefly complete cardiac arrest in one and possibly two instances. A characteristic record of ventricular fibrillation was also obtained by Halsey[2] in 1 case at the time of death, while Hoffman[3] has published a record which he interprets as indicating the brief occurrence of ventricular fibrillation terminating in recovery at the end of an attack of paroxysmal tachycardia. His interpretation is questioned by Lewis,[4] Hart[5] and others.

These few records constitute the entire direct evidence that ventricular fibrillation occurs in man. The belief of its occurrence beyond this evidence is based upon conjecture and analogy to experimental results. The question of its occurrence and its importance as a cause of sudden death has been discussed by Lewis,[4] who says that he has the strongest *a priori* grounds for the belief that sudden death results from ventricular fibrillation in many patients. He points out that when the ventricles fibrillate the coördinate beat of these chambers is lost; the muscle is divided up into small areas which show independent activities. This type of activity is functionally entirely ineffectual and the cardiac output ceases, the blood-pressure falls to zero and the circulation comes to a stand-still.

The observations to be reported here were made on a patient who had a series of attacks of prolonged cardiac syncope, closely resembling Stokes-Adams syndrome, from which she recovered. An electrocardiogram obtained during one of these attacks is typical of ventricular fibrillation, and it seems likely that all syncopal attacks were of the same nature. This observation represents, therefore, recovery from at least one relatively prolonged period of ventricular fibrillation, and probably recovery from several such periods.

F. B., a woman, aged forty-five years, was admitted to the Barnes Hospital December 29, 1915, complaining of shortness of breath, swelling of the feet, weakness, and cough. The family history is irrelevant. She had had three attacks of rheumatism at the ages of fourteen, twenty and thirty years, and had chorea at nine years. She had also had typhoid fever in childhood and scarlet fever at twenty years of age. During her first attack of rheumatism she was told her heart was affected. There was no history of a surgical operation nor any evidence of syphilis.

She has been short of breath on exertion as long as she could remember, and had been very pale and "anemic" for fifteen years. Swelling of the feet had been present for about one month, during which time dyspnea became more marked. She had slept with her head elevated for many years, but had been coughing for only about three or four weeks. She had had polyuria for about a year. Physical examination revealed a very pale, fairly well-nourished woman, who seemed in no great distress or danger. Slight cyanosis was observed. The heart was slightly enlarged. The apex beat was in the fifth interspace, 12 cm. to the left of the midsternal line. The cardiac dulness extended 3 cm. to the right and 13 cm. to the left of the midsternal line. There was a presystolic thrill over the apex as well as a presystolic and systolic murmur. The heart rate was 81 per minute and regular. Five moist rales were heard over the bases of the lungs posteriorly. The liver was not palpable. A pelvic tumor was present, and there was slight edema of the feet, legs, and thighs. The systolic blood-pressure was 138 mm. Hg., diastolic 72 mm. Hg. The blood examination showed 2,944,000 erythrocytes and 29,200 leukocytes per cubic millimeter. Hemoglobin, 30 per cent. (Sahli instrument). Albumin and casts were found in the urine. The excretion of phenolsulphonephthalein amounted to 43 per cent. in two hours. During the first six days in the hospital the patient's condition improved somewhat and she seemed in a fairly satisfactory condition. The pulse ranged from 75 to 100 beats per minute. The temperature was slightly elevated at first, but gradually subsided. A blood culture remained sterile.

On January 4, 1916, a pelvic examination was made per rectum. Shortly after the examination the patient was observed by the nurse to become suddenly unconscious "for a few minutes." She made jerking movements of her arms. The eyes were closed and the pulse was imperceptible. The intern was called immediately, and when he arrived the pulse was weak and irregular. The patient was very blue and the feet were cold. The pulse became regular in a few minutes and beat fairly strong at a rate of 68 per minute. The area of cardiac dulness was not increased. The presystolic and systolic murmurs were heard at the apex region as before. There was a hemorrhage in the conjunctiva of the left eye. The mental condition was clear and the patient was not suffering.

About one hour later, at 2.48 P.M., the patient was observed by the intern to become suddenly unconscious when electrocardiograms were being taken. The pulse disappeared from the wrist and the patient became very cyanotic. Breathing except for occasional gasps ceased for a period estimated at two or three minutes. The heart beat was inaudible at the apex. The heart beat returned after being apparently absent for about four minutes, and in about fifteen minutes the heart was beating almost regularly at a rate of 85 to 100 per minute at the wrist. During this time the breathing was slow, deep, and snoring. The arms and feet were frequently

stiffened out in convulsive-like movements. The reflexes of arms and legs were active. Pupils were pin-point in size, and there were irregular ocular movements.

At 5 P.M., two hours after the onset of unconsciousness, the patient became very noisy. She was still unconscious, but tossed her arms, head, and feet about continually. She became quiet at 7 P.M., and at 8.30 P.M., although still unconscious, she was breathing quietly, at times suggestive of Cheyne-Stokes breathing. The pulse was irregular, about 80 per minute. The thrill could not be felt, and the heart sounds were very confusing to the ear.

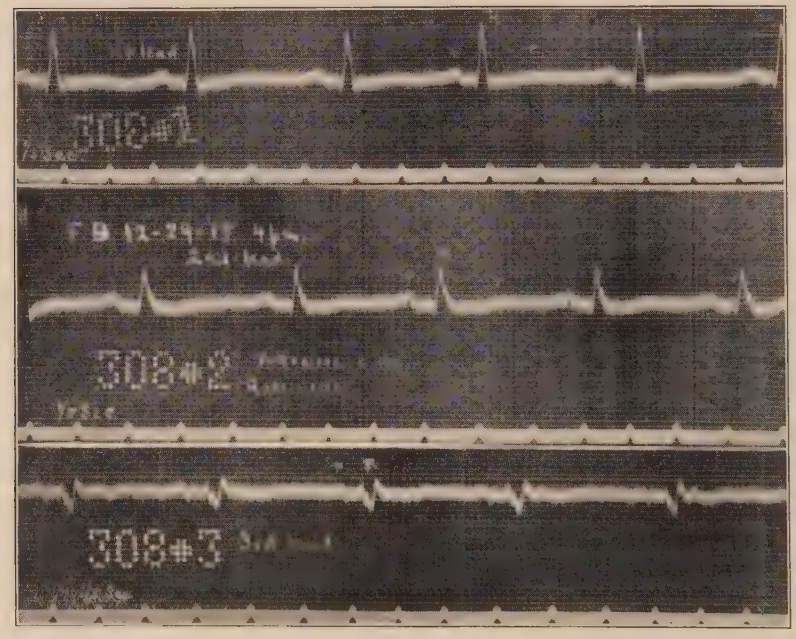

FIG. 1.—Three usual leads, obtained on day of admission, December 29, 1915.

At 11 P.M. the patient had her third convulsion. She became suddenly cyanotic and the heart beat became inaudible. Breathing ceased for four minutes, the heart sounds disappearing before breathing stopped entirely. The breathing returned slowly, at first only three or four per minute, and then gradually increasing up to 20 per minute. The heart beat returned very slowly with an increasing rate. The heart rate in successive minutes was 27, 41, 35, and 45. The rate remained at about 56 per minute.

The following day, January 5, the patient was dazed but not delirious. She could answer questions intelligently, but was slow to recognize objects

and people. The pulse remained very irregular and the heart sounds suggested myocardial weakness. Examination of the lungs and liver were negative; 1 mg. strophanthin was given at 9.50 A.M. At 2 P.M. fluid began to collect in the throat, which was expectorated with difficulty. Edema of the lungs developed and the patient died at 9.15 P.M. January 5, the heart remaining unchanged.

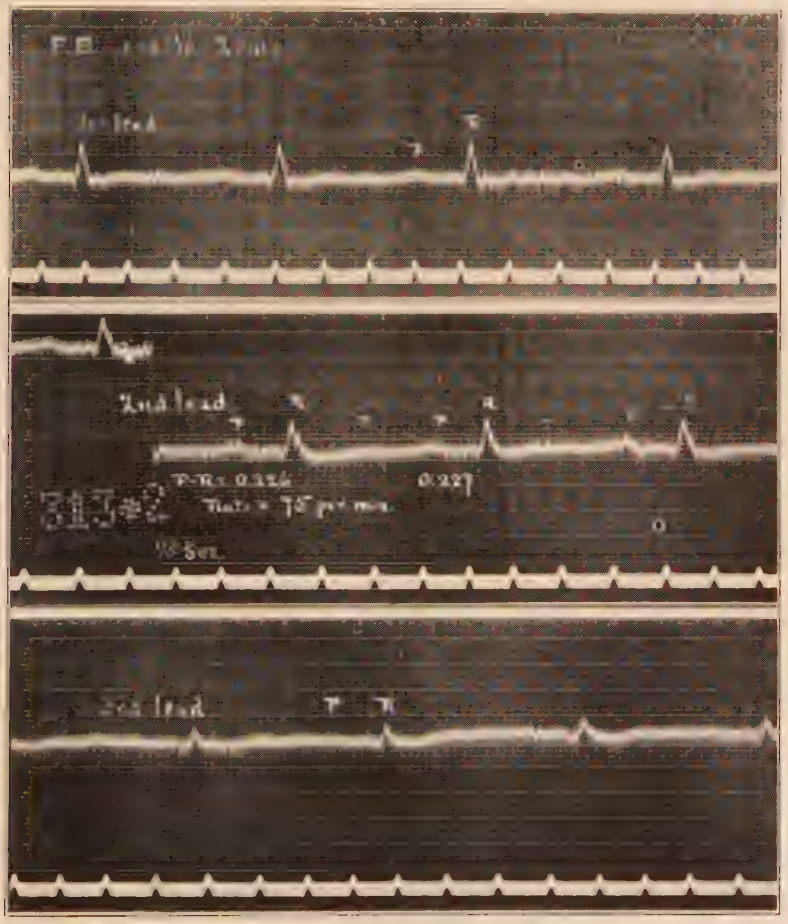

FIG. 2.—Three usual leads, January 4, 1916. Eight minutes before onset of ventricular fibrillation.

Electrocardiograms were made before, during, and at frequent intervals after one attack of unconsciousness. The records obtained on the day of admission (Fig. 1) show the normal cardiac mechanism, with complexes

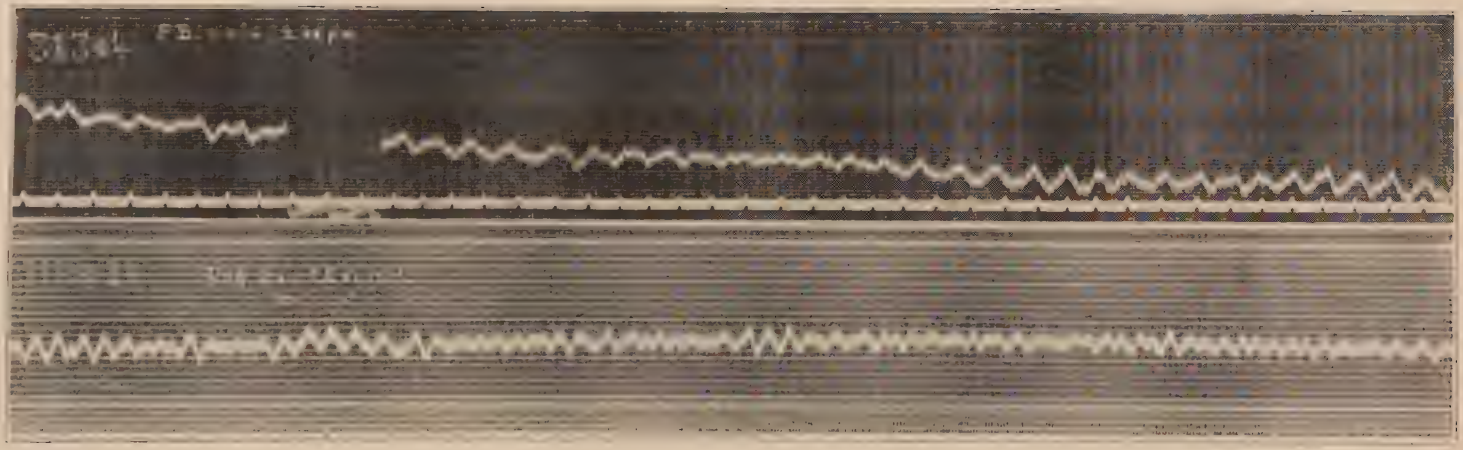

FIG. 3.—Upper curve. Record obtained during period of cardiac syncope at 2.48 P.M. Second lead. Lower curve from dog. Ventricular fibrillation observed in the exposed heart. Lead from right foreleg and left hindleg.

of the form suggesting moderate left-sided predominance. They indicate no delay in the auriculoventricular conduction time. The heart rate was 100 per minute. The first record obtained on January 4, eight minutes before the second attack of unconsciousness, shows complexes nearly similar in form to those previously obtained except that the A–V conduction time is now prolonged, the P–Q interval measuring 0.226 second (Fig. 2). The record obtained during the attack of unconsciousness at 2.48 P.M. is typical of ventricular fibrillation, as is shown by the curve which accompanies it, from a dog whose fibrillating ventricles were exposed by operative procedures (Fig. 3).

The next record was taken seventeen minutes later, at 3.05 P.M., and showed the heart beating regularly at a rate of 61.5 beats per minute.

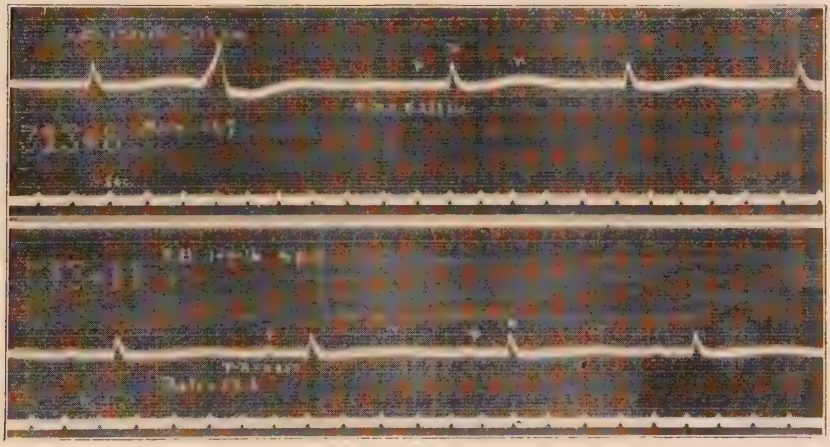

FIG. 4.—Curves obtained twenty minutes and seventy-two minutes respectively after the second period of ventricular fibrillation.

At 3.18 the record (Fig. 4) shows the heart beating at a rate of 57 beats per minute. The second lead is shown, and it is quite similar in form to that seen in the record obtained on the day of admission. Several unusual complexes occur, however, one of which is shown, a tall broad-based complex occurring prematurely. The P waves are inconspicuous and perhaps diphasic. Records obtained every few minutes after this one showed very little change. That obtained at 4 P.M. (Fig. 4) shows the heart beating regularly, 53.6 beats per minute. The P waves have become well defined and no abnormal complexes appear. There is a distinct delay in the A–V conduction time. At 8 P.M. the heart was beating irregularly (Fig. 5). Ectopic premature ventricular contractions, yielding constantly varying complexes, were occurring after every normal beat. There was no delay in the A–V conduction time. The auricles were also beating irregularly.

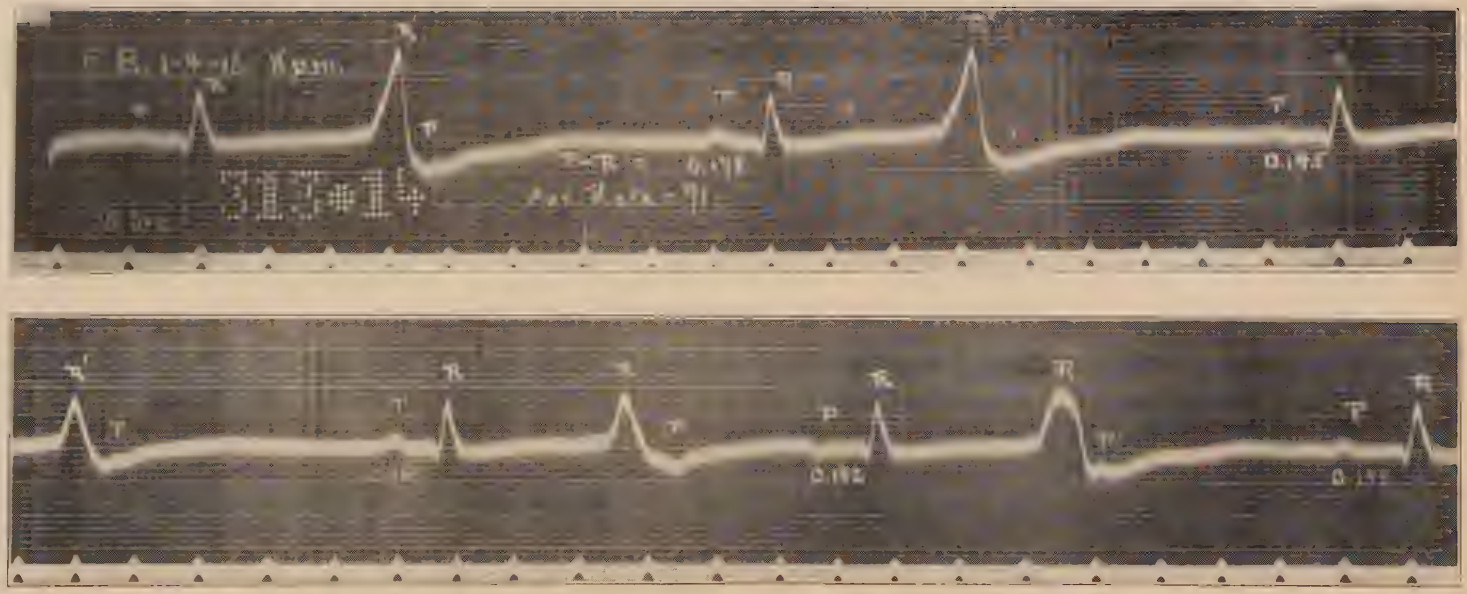

FIG. 5.—Obtained five hours after the period of ventricular fibrillation. Various abnormal complexes are seen.

No records were obtained at the time of the third period of unconsciousness and convulsive seizure. At 9.45 A.M. on January 5 records were obtained immediately before the intravenous injection of 1 mg. of strophanthin (Fig. 6). The three leads are shown and indicate that the cardiac activity was much as it had been the night before, abnormal complexes following all normal complexes. The form of the abnormal complexes show further changes, however.

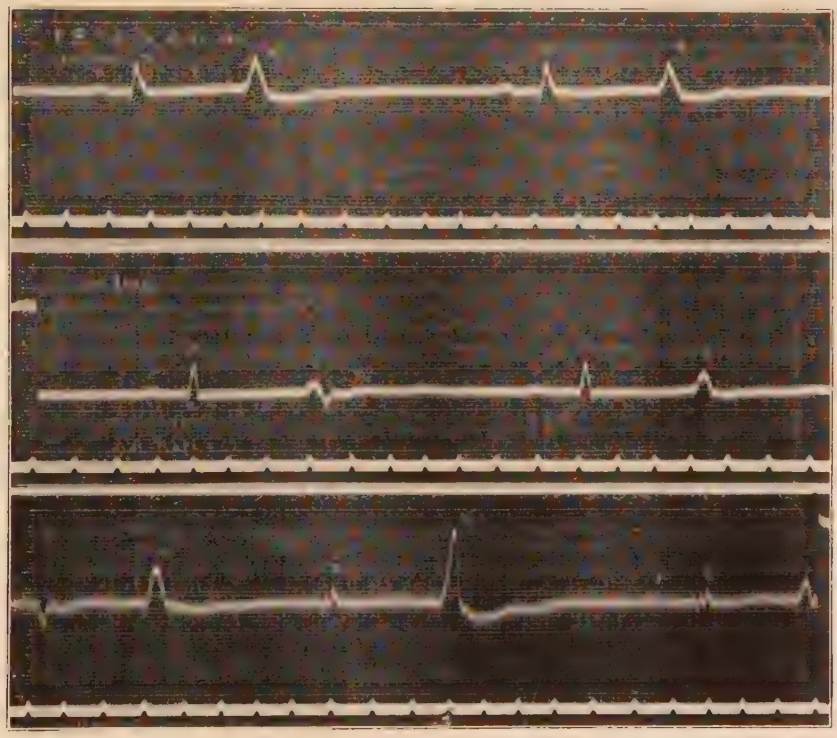

FIG. 6.—Three usual leads. Twenty hours after the period of ventricular fibrillation, immediately before strophanthin was administered.

The record obtained at 10 A.M., ten minutes after the strophanthin was given, shows many abnormal ventricular complexes following one another in rather rapid and irregular succession (Fig. 7). Only one sequential beat appears. This record indicates that numerous points in the ventricles were generating stimuli which spread over various paths through the ventricles. This record is of interest as regards the relation of the cardiac activity which it represents and fibrillation, as has been shown in experimental ventricular fibrillation, a point that will be referred to later.

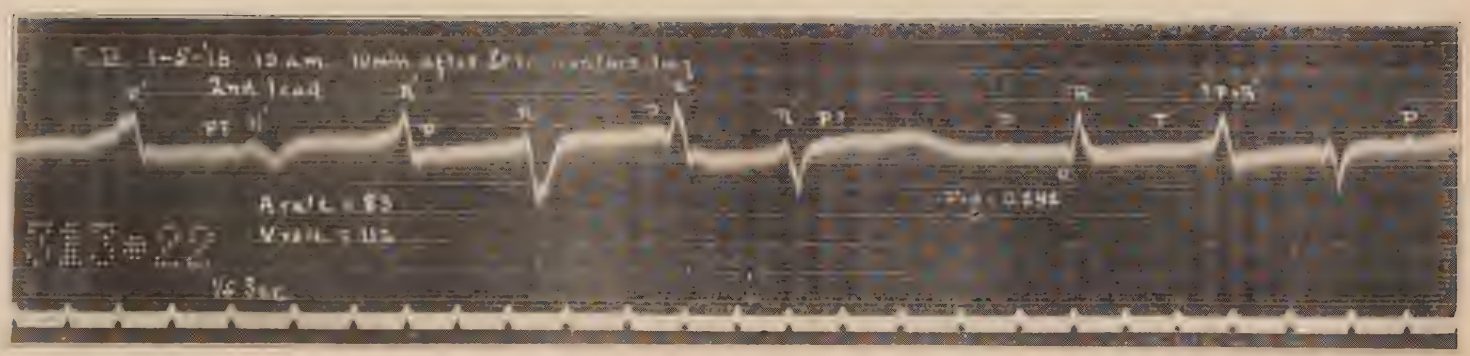

Fig. 7.—Record obtained immediately after the intravenous injection of strophanthin.

Fig. 8.—Record obtained twenty-one hours after the period of ventricular fibrillation.

The last record was obtained at 11.40 A.M., about nine hours before death, when the auricles were beating at a rate of 123 beats per minute (Fig. 8). Partial heart block and ectopic premature ventricular contractions occurred. The sequential beats yield complexes, however, quite similar to those obtained when the patient first entered the hospital, and so far as this evidence goes the occurrence of ventricular fibrillation produced no change which caused alterations in the sequential ventricular complexes.

Autopsy No. 587, the notes from which we are indebted to Dr. Opie.

Anatomical Diagnosis. Bilateral carcinoma of the ovaries. Chronic fibrous endocarditis of the mitral and aortic valves. Hypertrophy of the left auricle and of the right auricle and ventricle. Chronic passive congestion of the liver and spleen. Edema of the lungs. Bronchopneumonia. Peritoneal effusion. Chronic diffuse nephritis, with granular kidneys of normal size. Old pleural adhesions. Arterial sclerosis. Healed tuberculosis of the bronchial lymph nodes.

Heart weighs 290 grams. Upon the surface is a scant amount of fat which has a translucent edematous appearance. The heart muscle is firm and red brown in color. The thickness of the left ventricle is 16 mm. The left auricle has thickened walls measuring 2 mm. The endocardium has a gray, thickened appearance. The right ventricle is thickened, measuring 4 mm. The right auricle is also somewhat thickened. The mitral orifice measures 8 cm. The valve is thickened and the segments are fused together, so that the valvular orifice is contracted. The valve segments are firm. The free edge is rounded and retracted. Just above the free edge there are several projecting vegetations. The chordæ tendineæ are thickened and shortened. The aortic orifice measures 6.7 cm. The semilunar folds are intact, but the free edges are slightly thickened and rounded, particularly in the neighborhood of the carpora aurantia, from one of which there is a small projecting vegetation. The tricuspid orifice measures 11 cm. while the pulmonary orifice measures 7.7 cm. These valves are normal. The main branches of the coronary arteries are patent. An occasional elevated yellowish area occurs in their lumen. The thoracic and abdominal aorta is thickly studded with elevated plaques usually 0.5 to 1 cm. across, of yellowish color.

Microscopic examination of the heart muscle of both auricles and ventricles fails to reveal any distinctive lesion. The muscle fibers have a loose appearance, as though separated by fluid, and there is moderate fragmentation. There is a slight, general, small round-cell infiltration.

The autopsy throws no light upon the cause of the ventricular fibrillation. It has been shown by Lewis[6] that obstruction to the blood flow through the coronary arteries in animals may result in ventricular fibrillation. The moderate grade of sclerosis of the

coronaries in the case reported indicates, however, that the coronary blood supply was probably not materially interfered with, although the presence of vegetations on the mitral and aortic valves permits of the possibility of a coronary embolus which escaped detection at autopsy. The definite signs of cardiac insufficiency suggest the possibility of improper blood supply of the heart muscle as one of the results of this insufficiency. This may have been a factor in the production of the transient fibrillation of the ventricles.

Levy[7] has described an effect of light chloroform anesthesia which renders the ventricles specially prone to fibrillation. Ventricular fibrillation is then readily produced by the injection of adrenalin. The fibrillation produced by this method is always preceded by a stage of complex ventricular irregularities. Levy believes that fibrillation is a still more advanced and complex grade of these ventricular irregularities. They have been studied by means of electrocardiograms by Levy and Lewis,[8] who have shown that the ventricular irregularities preceding fibrillation consist in ectopic ventricular contractions arising from numerous foci. They consider this type of derangement of the heart beat as a transitional stage toward ventricular fibrillation and have observed it also after recovery from fibrillation. Levy has called this condition when ectopic beats arise from multiple foci in the ventricles a state of potential fibrillation. The electrocardiogram shown in Fig. 8, obtained immediately after the injection of strophanthin, is similar to those obtained by Levy and Lewis during this period of so-called potential fibrillation.

Much light has been thrown on the functional derangements of the heart which underlie fibrillation by the work of Mines[9] and of Garrey.[10] The former has studied the effect of successive induction shocks upon the frog's heart and found that under certain conditions which allow the muscle to respond to a rapid series of shocks, the refractory period of the muscle becomes shortened and the rate of propagation of the wave of excitations becomes slowed. Mines advanced the hypothesis explaining fibrillation based on these observations. He believed that when these changes occur a portion of the ventricular musculature goes very briefly into contraction and the refractory period of this particular portion passes off

before the impulse which travels slowly through the ventricular musculature again reaches it. Then this portion can go again into contraction. He suggests that such a circulating rhythm may constitute the condition known as ventricular fibrillation.

Garrey[10] has carried the knowledge of the nature of fibrillation further, and by an ingenious experiment has been able to observe directly the passage of waves of muscular contraction through the heart muscle which continued uninterruptedly to effect successive portions of the muscle, returning again and again to the same portion. His experiments form an adequate basis for his belief that fibrillary contractions of the heart muscle depend on the establishment within the musculature of multiple regions of block or reduced conductivity. The impulses thus blocked or delayed take abnormal and circuitous paths, and return to the same portion of the muscle after the refractory state has passed off but while other portions are still refractory. The latter portions are subsequently involved in a similar manner, and the whole tissue mass is thus thrown into a continuous incoördinated contraction, which is not initiative or sustained by new impulses arising from any definite location.

The electrocardiograms of the patient here reported obtained after the attack of fibrillation indicate that there was present in the ventricles functional abnormalities which apparently predispose to fibrillation. The abnormal ventricular complexes which vary greatly in form indicate that cardiac impulses were arising in various points in the ventricles and that these impulses were traveling through the ventricular musculature along abnormal paths. Many of these complexes are remarkably prolonged, especially in their initial phase, indicating that the impulses were passing through the musculature at an abnormally slow rate. These abnormalities are indicated most strikingly in the record obtained just after the injection of 1 mg. of strophanthin. The fact that the drug apparently brought the heart more definitely into the so-called state of potential fibrillation seems worthy of emphysis in view of the fact that sudden death, perhaps from ventricular fibrillation, has not infrequently occurred after the use of this drug. We have recently had one such experience, and a number of others have been reported to us verbally.

It seems probable that ventricular fibrillation is prone to occur in hearts in which there is a disturbance of the conduction of the impulse of the heart beat through the ventricles. Such a disturbance would tend to produce the conditions which Mines and Garrey have described as underlying fibrillation. A disturbance of intraventricular conduction may be detected by means of electrocardiograms, as has been recently pointed out by one of us,[11] and when such a disturbance is present it should be taken as a contra-indication for the use of such drugs as chloroform, adrenalin and strophanthin, which predispose the heart to ventricular fibrillation. The case of sudden death which we observed after strophanthin yielded electrocardiograms suggesting such a disturbance, but unfortunately at that time we had not come to recognize their significance.

There is no direct indication as to why the heart in the case here reported should have recovered after ventricular fibrillation became established. The ventricles were relatively small, and would therefore be more likely to recover than those of a larger heart, as Garrey has shown that there is a definite relation between the size of the muscle mass involved and recovery. It is well known that recovery from ventricular fibrillation is not uncommon in smaller animals, as Gunn[12] has shown for at least one type of fibrillation in the rat. The larger the species or the larger the animal of a species the less likely is recovery from ventricular fibrillation to occur. This case is the first example of recovery from well-established ventricular fibrillation that has been observed in man.

SUMMARY. A case is reported which showed marked cardiac insufficiency and which had three attacks of cardiac syncope. During one of these attacks an electrocardiogram was obtained which is typical of ventricular fibrillation. The patient lived thirty hours after this syncopal attack and numerous electrocardiograms were obtained during this time. One immediately after the intravenous injection of strophanthin showed a deranged cardiac mechanism similar to that observed experimentally by Levy and Lewis during the so-called state of potential fibrillation. The abnormal forms of ventricular complex which occurred frequently, were such as to indicate that there was a derangement of intraventricular

conductivity. This may have been the prime factor in the production of the ventricular fibrillation. The occurrence of ventricular complexes indicative of derangement of intraventricular conductivity should be taken as contra-indication for the use of drugs such as chloroform, adrenalin and strophanthin, which predispose the heart to ventricular fibrillation.

The foregoing case is the first example of recovery from well-established ventricular fibrillation that has been observed in man.

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GASTRIC POLYPOSIS

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AND

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Gastric polyposis is a sufficiently rare disease to be of considerable interest. During the past year 2 cases of this affection and an unusual specimen have come under our observation which we wish to report briefly.

Case I.—G. C. D., male, aged fifty-five years, was admitted to the Union Protestant Infirmary November 1, 1915, complaining of weakness, anemia, and loss of flesh. Three months before admission the patient was suddenly taken with a severe chill followed by fever. A blood examination revealed malarial parasites for which quinine was adminstered. The patient had lost twelve pounds in weight during the last three months. He had no pain, no digestive disturbance, but occasionally felt some discomfort in the lower abdomen. The bowels were regular but the stools were continuously tar-colored.

Physical examination revealed a well-developed, well-nourished man. The skin and mucous membranes are decidedly pale. There is no jaundice. The lungs and heart are normal. The abdomen is soft; there is no tenderness anywhere; no rigidity; no masses; no free fluid in the abdomen. The edge of the liver is palpable; there are no enlarged glands. The contents of the stomach obtained after a test meal contained considerable mucus, and there was an entire absence of free HCl, with a total acidity of 4, and an absence of lactic acid. A retention meal failed to reveal any evidence of the rice taken the evening before. The stools are dark in color and contain large quantities of occult blood. The blood examination reveals a marked secondary anemia, presenting 2,200,000 red cells; the hemoglobin varied between 37 and 55 per cent.

The roentgen-ray examination with a bismuth meal presents a cow-horn stomach of normal size with a very large, persistent filling defect at the junction of the greater curvature and pylorus; there is no obstruction.

On account of the constant bleeding, which was at all times revealed in the stools, the absence of free HCl in the gastric contents, together with a very large and constant filling defect as revealed by the roentgen rays, the diagnosis of carcinoma of the stomach was made, notwithstanding the fact that the patient had lost but little flesh and had no pain or gastric disturbance.

Operation was advised and was performed November 18, 1915. Upon opening the abdomen a soft tumor, the size of a hen's egg, was palpated on the greater curvature of the stomach near the pylorus. An incision was made on the anterior wall of the stomach and a papillomatous mass with a broad base was observed springing from the posterior wall near the greater curvature. The surface was rough, ulcerated, and hemorrhagic, with numerous papillæ; it was about 7 cm. long, 4 cm. wide, and 5 cm. high. No other tumors were observed in the stomach. The tumor was excised with the electric cautery by making an oval incision around the base, including a good margin of normal tissue.

The patient made a rather uneventful recovery from the operation, but the stools continued to present occult blood. The hemoglobin was constantly low.

The pathological report of the growth indicated that it was an adenopapilloma. Cancerous changes were revealed in the base of the growth.

Inasmuch as the patient's general condition did not improve and his anemia continued to increase, as well as on account of the constant appearance of blood in the stools even after numerous transfusions, further exploration was decided upon.

The operation was performed April 6, 1916. The stomach was found in good condition. The duodenum was found adherent to a mass posteriorly, which had apparently eroded into the duodenum. The mass was about the size of a hen's egg and densely adherent to the abdominal aorta and vena cava. Numerous palpable glands were felt throughout this region. The mass was definitely malignant and its removal impossible. The patient recovered from the operation, but the anemia became more progressive and the stools continued to reveal blood.

Notwithstanding numerous treatments with radium the patient continued to lose flesh and strength, and died of exhaustion October 2, 1916.

Case II.—G. T. T., aged fifty years, was admitted to the Union Protestant Infirmary March 23, 1916, with a history of indigestion, with which he was first affected nine months ago. There was present pain, fulness, nausea, and vomiting. He had lost twenty-five pounds in weight. There was no history of hematemesis or melena.

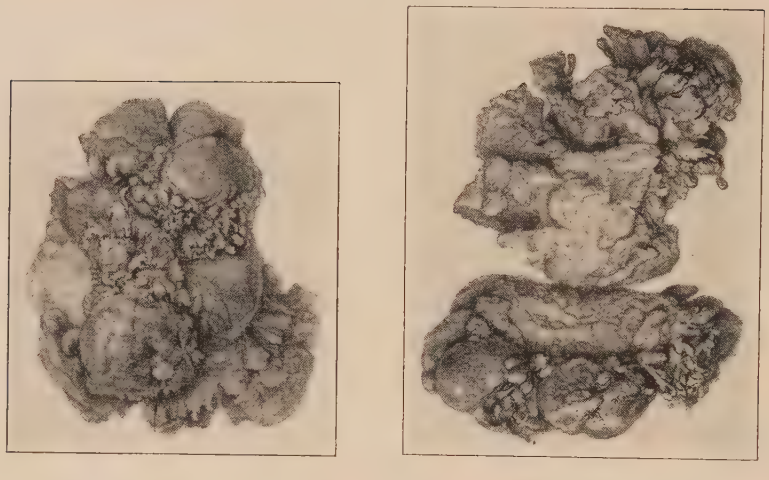

FIG. 1.—Case I.

FIG. 2.—Case II.

On examination the patient is found poorly developed and undernourished. The liver is somewhat enlarged. In the epigastrium there is a sausage-shaped mass moving with the respiration and not tender to pressure. A radiographic examination reveals a large filling defect of a crater-like appearance at the pylorus, indicating an annular carcinoma of the pyloric ring; there is also marked retention (twelve hours). The gastric contents is brownish in character, containing mucus and blood, presenting an absence of free HCl, but with a marked lactic acid reaction. The retention meal is positive; the stools contain blood.

A diagnosis of pyloric carcinoma with stenosis was made and operation advised. This was performed by Dr. Chaffee, resident surgeon of the Union Protestant Infirmary, March 26, 1916. On opening the abdomen a large mass presented itself at the pylorus. The tissue was hard and did not give the impression of being carcinomatous, but one enlarged gland was observed. A resection of the stomach containing the mass was made and a posterior gastro-enterostomy performed. The patient made a satisfactory recovery.

On incising the resected mass a papilloma revealed itself just within the pylorus, projecting into the lumen so as to nearly occlude the orifice. The base of the growth is hard, indurated, and 3 cm. in diameter; that portion of the papilloma projecting into the pylorus is much softer and is 3 cm. in length. The sections made from the polyp present the typical appearances of malignancy. The carcinoma is of the medullary type in the papilloma and the scirrhus type in the stomach wall.

Of interest in this connection is a specimen found in the museum of the College of Physicians and Surgeons of Baltimore, presenting a typical example of multiple papilloma involving almost the entire stomach. It is interesting to note that that portion involving the pylorus has undergone a malignant degeneration.

A most exhaustive study of gastric adenopapillomata was published by Epstein in 1864, in which he collected 14 cases in 600 autopsies; he also collected 8 other cases from literature. Of these 22 cases 12 are solitary and the other 10 consisted of nine small and one large polyp.

As regards etiology, most authorities point to a chronic gastritis as an underlying factor in the production of gastric adenopapillomata. The disease is more apt to occur in males than females, and in most instances after the fortieth year of life.

There are great variations as to the number of polypi that may be present, varying in individual cases from 100 to 200. They may also vary as to size from that of a pea to a hazelnut, and may be as much as 2 or 3 cm. in length. They usually present a reddish or grayish aspect and are rather soft in consistency.

Fig. 3.—Case III. Specimen in museum of College of Physicians and Surgeons, Baltimore.

They are frequently pedunculated or attached by broad bases, or often club-shaped or cylindrical and frequently pigmented; the color depending upon the degree of vascularity. These growths may take their origin from any part of the gastric mucous membrane, the membrane covering them being smooth or villous.

The usual location of the growths is at the pylorus, although any portion of the stomach may be involved.

According to Menetrier there are two distinct types of gastric polyps depending upon whether the hypertrophy and hyperplasia involve the excretory or the deeper portions of the tubular glands. In the first type lobulation is more apparent and cystic forms are more common, the orifices of the excretory ducts being obliterated by the growth of the interglandular connective tissue. In the second type, those in which the deeper portions of the glands are involved, the polyps are uniform and tubulation is less pronounced. Between the two forms of polyadenomata there are a number of intermediate types; these mixed types are most common.

The mucous membrane not involved in the disease may present the appearance of a chronic gastritis. It may be congested, presenting hemorrhagic erosions with pigmentation. The polyadenoma "en nappe" of Menetrier is much less common. In this variety the hypertrophy and hyperplasia involve the entire mucous membrane in a certain area, thus developing into large plaques, and not as simple polypoid vegetations.

Microscopically polyps consist, according to Meyer, of hypertrophied mucous membrane muscularis mucosa and a connective-tissue core containing fairly large bloodvessels. The polyp presents on section three lobules, each of which contains a part of the core, here consisting of connective tissue and muscularis mucosa. The hypertrophied mucous membrane contains enlarged glands with dilated lumens. The glands are surrounded with columnar cells with basal nuclei; a large number of goblet cells are present, secreting mucus into the lumen of the gland. The interstitial tissue between the glands contains lymphoid cells, plasma cells, eosinophiles, and polynuclear leukocytes.

Inasmuch as polypi of the stomach are usually benign in character they may be present for a long period of time without producing symptoms. In fact this affection is most frequently so obscure that a correct diagnosis is only revealed at operation or at autopsy. In some instances the symptoms are extremely severe; there may be present intense anorexia, edema, and ascites, producing a symptom-complex much like that of cirrhosis of the liver. Occasionally a

diagnosis is made possible by the finding of a fragment of a polyp in the wash-water during lavage, such as was observed in Meyer's case, and at times by the presence of a large polyp in the stools. In the extensive forms of gastric polyadenoma, roentgen-ray, examination is often very conclusive. There is, according to Meyer, a "mottled appearance of the entire right half of the stomach, as if the bismuth were trickling through and around numerous masses together with the irregular and indefinite outline of the stomach." The condition may be mistaken for an achylia gastrica, inasmuch as polyps of the stomach are usually associated with absence of gastric secretion; the great excess of mucus, however, together with the unusual character of the mucus, of the peculiar egg-white appearance, distinguish this condition from an achylia gastrica. A most important and constant finding, too, is the presence of fresh blood appearing constantly in the gastric contents, especially, as Meyer points out, when observed in cases of achylia gastrica with normal or increased gastric motility, inasmuch as in those cases of hemorrhage due to ulcer there is usually hyperacidity with diminished motility.

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DISCUSSION

Dr. Thayer said that twenty-five years ago he had seen a very interesting instance of this kind. He had been called out of town to see a lady between sixty and seventy years old who presented a picture of pyloric obstruction. She had been vomiting continuously; had a very greatly dilated stomach; was thin, pale, looked like a woman with a malignant neoplasm; and had a distinctive, palpable pyloric tumor, which, upon examination, proved to be a little larger than a horse-chestnut, well felt through the thin abdomen. No examination of the gastric juice had been made, the case being one in a country town and the appliances not at hand, but it seemed clearly a case of pyloric obstruction, due to a malignant neoplasm, although no mestastasis could be made out. She died some weeks after; he had been away, and the attending physician sent him the stomach. It presented a single type of adenomatous polyp, with quite a long pedicle, which engaged in the pyloric orifice so as to cause an almost complete obstruction. In the polyp, an alcoholic specimen sent him about the size of a horse-chestnut, microscopic examination showed no evidences of carcinoma at all. It was apparently a death from obstruction by the engaging of a benign polyp in the pylorus.

Dr. Janeway said, in a case of this type seen a number of years ago in St. Luke's Hospital, the physical examination revealed a tumor of

the most extraordinary mobility of any abdominal tumor he had ever seen, about the size of an egg, which varied, on different days, anywhere between immediately beneath the ensiform in the epigastrium to the right iliac region, and never, on any two successive days, in the same portion of the abdomen. The patient had obvious symptoms of carcinoma of the stomach, but he and his associates were rather at a loss to interpret the extreme variability in the location of the tumor. It was proved to be a pedunculated adenocarcinoma of the stomach, which hung free by quite a long pedicle in the interior of the stomach, and its extreme mobility was in this way explained. He asked Dr. Friedenwald whether he had observed any unusual mobility of the mass in any of his cases.

Dr. Friedenwald (closing) said they had not observed any unusual mobility of the polypoid mass; but Dr. Finney had had a case some years ago, at the Johns Hopkins Hospital (but unfortunately the specimen and the history were both lost). He and the speaker had vainly tried to resurrect specimen and literature, but to the best of Dr. Finney's recollection it was a case in which a patient had a polyp which entered the pylorus and would, at times, constitute a complete obstruction and then fall back into the stomach again and the patient would digest well, when suddenly he would again be taken with symptoms of pyloric obstruction which would last a day at a time and then disappear.

PAROXYSMAL TACHYCARDIA OCCURRING IN CHILDREN

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NEW YORK, N. Y.

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Simple paroxysmal tachycardia occurring in children below the age of ten years is admittedly rare, especially if unaccompanied by valvular lesions of the heart. The cases which form the basis of this communication are few, but they are only possible from a very large number of cases, and have the virtue of being among the youngest thus far reported, and for this reason are most instructive. In one case at least there is a clue as to the possible origin or causal factor of this condition. In these children not only is the picture of the disease fully developed, but also, in spite of its severity, the cases show many points of approach to the adult cases, at the same time points of difference which make them studies of great interest. Lewis in his 45 cases of tachycardia, accompanied or unaccompanied by cardiac lesions, either of valves, muscles, or arteries, mentions only one case below ten years of age, that of a child aged six years. He states the actual age limits as six to seventy-five years, the highest incidence twenty to thirty years, the disease occurring more frequently in the male sex. I will not enter here into the general history of paroxysmal tachycardia, which is founded upon the phenomenon as seen in the adult, such does not interest us now. There is no communication, excepting isolated cases, in the literature on this condition as it occurs in children. I am inclined to the belief that the condition is not so rare among children as we would be led to believe from the fact of its dearth of a literature. The new

instruments of precision in the study of cardiac disease must in the future bring to light new cases which will give us a more definite idea of its frequency and other facts which are now unobtainable. My own cases came to me quite accidentally in the course of an uncommonly large cardiac material, and I have been aided in fixing the authenticity of the clinical diagnoses by means of cardiogram tracings. These tracings were made in the cardiogram laboratory of the Mount Sinai Hospital under the direction of Dr. B. S. Oppenheimer. The first case, which is the youngest on record, is clinically of great interest, inasmuch as the child came to me with a history that two weeks before the condition in which I saw him he had suffered from a faucial angina of some duration; he had not made a prompt recovery, but had suddenly, after a tedious convalescence, passed into the condition which I will describe.

Case I (October 21, 1915).—A. A., male, aged twenty-two months; an only child; father and mother healthy young people; mother had no miscarriages; normal delivery; fed on the breast for eleven months. When an infant had laryngismus stridulus; two weeks before the present illness he was ill with angina and bronchitis; when brought to me had been in this state for a day or more. He was much cyanosed and there was a general edema over the surface of the body; there was great dyspnea; the patient lay curled up on his side, which was the only position in which he could catch his breath with comfort. The examination of the lungs showed dulness and increased vocal resonance over the lower lobe behind the right lung. The liver was felt enlarged and soft some distance below the free border of the ribs; the spleen was much enlarged; the pulse could be counted at the wrist, but over the apex varied from 224 to 280; the dyspnea was great. The case acted on the first visit in the manner seen in sudden cardiac failure in infectious diseases, such as that in pneumonia of children or complicating diphtheria. The prognosis was placed seriously, and his physician advised to administer digipuratum intravenously. After a few days the heart quieted down, became slower, and in four weeks not a trace of the above attack was left. It seemed as though the boy had been saved by the prompt treatment. Two months after the attack the father noticed that the patient had spells of "cardiac irregularity" or palpitation, and with the coöperation of his physician (Dr. Doughty)

I took him into my hospital service for future study The subsequent history is best told by the hospital entries:

January 30, 1916. *Physical Examination.*
General condition: Child, very well nourished; color good.
Head: Frontal and parietal bosses.
Eyes, ears, nose: Negative.
Mouth: Tonsils enlarged but not inflamed. Throat and tongue clear.
Neck: No rigidity.
Glands: No adenopathy.
Chest: Moderate beading of ribs and Harrison's groove. When child cries there is marked inspiratory recession of the lower sternum and xiphoid.
Lungs: Clear.
Heart: Not enlarged; sounds of good force and quality. No murmurs.
Pulse: Equal; regular; good volume and tension.
Abdomen: Relaxed.
Liver: Edge felt one finger below ribs.
Spleen: Not felt.
Genitals: Negative.
Extremities: Knee-jerks.
Synopsis: Frontoparietal bosses; beading of ribs; Harrison's groove; depression of lower sternum.

February 2. This morning patient was in a quiet condition after a slight crying spell; has pulse rate of 288. Slight edema of eyelids. While in an apparently quiet condition and playing, 240. A third count makes it 270. Slight edema of surface. No enlargement of liver. No cyanosis. In a second crying spell the pulse was 126.

12.30. Crying. Heart rate 104; slowing especially on strong inspiration.

February 3. Electrical galvanic test: AO and AC greater than KO and KC. AC and AO at $1\frac{1}{2}$ milliampères. Tetanus with AO and AC of $3\frac{1}{2}$ milliampères.

February 3. Electrocardiograms are normal in an interval of tachycardia.

February 4. During a crying spell pulse rate was 132 per minute. Apex in sixth space 6 cm. from median line. Right ventricle 2 cm. from median line. No dulness behind sternum. Heart sounds normal.

February 1. Urinalysis: Acid; microscopically, negative.

February 2. Acid, 1030; microscopically, negative.

February 5. Roentgen-ray report: Roentgen examination of the chest does not show any definite evidence of an enlarged thymus. The heart is approximately normal in size and shape.

The patient was readmitted to my hospital service February 1, 1917, for further study, with the history that until October, 1916, he had been doing quite well, of course, under the care of

his physician, who had given him digitalis. The drug was not well borne, however, the pulse being depressed at one time below 60 per minute. Since October the patient had had five attacks of tachycardia, observed by the parents. At these times they had learned to know of the attacks, as the boy would complain of feeling tired and would lie down. During the preceding summer he had no attacks. A week before readmission he had a sharp pain in the precordium during the attack, with drowsiness.

Physical Examination. General condition: good; well nourished; not acutely ill.

Head, face, neck, eyes, ears, and mastoids: Negative.

Mouth: Tongue moist; coated; teeth good; tonsils both enlarged.

Chest: Expansion fair and equal.

Lungs: Anterior and posterior clear.

Heart: Normal in size and position. No murmurs or accentuations.

Pulse: Equal, regular; fair tension; normal rate.

Abdomen: Soft; rounded; generally tympanitic; ulcer; no masses; no rigidity.

Liver: Upper border, fifth rib; lower border, edge felt 3 fingerbreadths below costal margin.

Spleen: Not felt.

Kidneys: Not felt.

Synopsis: Palpable liver.

February 2. Pulse rate 270 (?); counting with stethoscope $\frac{1}{6}$ of a minute 43 to 45 (Dr. Koplik).

Apex during attack $7\frac{1}{6}$ cm. to left of median line; right side $3\frac{1}{2}$ cm. from midline.

Liver and spleen: Not palpable.

Color: Normal; no cyanosis; very slight puffiness under eyes. When undisturbed there is tendency of child to lie on side.

February 3. Pulse 168, quiet.

February 5. Pulse 108 by auscultation; patient sitting and happy.

February 6. Rate 96.

February 7. Tonsils enlarged, particularly on left side.

Electrocardiogram, February 2, 1917. The rate is 255 per minute. The tachycardia is regular, of auricular origin (auricular tachysystole). The *R* waves are small in lead *I*, normal in size in leads *II* and *III*. The wave which appears to be the *T* wave is upright in lead *I*, inverted in the other two leads. *P* and *T* cannot be positively identified.

Electrocardiogram, February 6, 1917, 498. The electrocardiogram shows a return to normal rate. The *T* waves in lead *I* and *II* are unusually tall and prominent. The *P* waves are also prominent and slightly angular. Except for the tall *T* waves the electrocardiograms are now normal.

Discussion. This case is remarkable, first having been observed in the primary attack after an attack of grippe, in which the symptoms were those of an acute break-down or weakness of the heart, with exceedingly rapid rate and signs of weakness of the heart in edema of the general surface of the body, cyanosis, swelling of the liver and spleen, and great dyspnea, as seen only in impending death. An improvement and apparent cure took place, and then a period of comparative comfort and freedom, followed by regular attacks of paroxysmal tachycardia of varying duration. One attack in the hospital lasting a few hours and another fully twenty-four hours. The spleen and the liver never enlarged to the extent in the subsequent as in the first attack. The cyanosis did not reappear nor did the general edema after the first attack. During the habitual attacks or paroxysms the boy was not uncomfortable. He would at times sit and play with a pulse rate of 204, at others would lie quietly in his crib, pale, eyelids slightly puffy, and say he felt tired. Otherwise between the attacks he impressed one as an exceedingly bright, active child of good color, with marks of early rachitis. It is possible in this case to assume that the first attack of influenza was the starting-point of his affection and that the cardiac collapse of the first attack was the forerunner of the subsequent attacks, and that in this case there was a serious involvement of the myocardium as the result of the influenza. A tachycardia was thus established on the foundation of an infective myocarditis.

Case II.—The second case which I have to report came under my notice when the patient was three years old. The previous history taken in my office states that as an infant her physician, when she was six months of age, told the parents the baby had a rapidly beating heart. This was brought to their notice every few months, and the symptoms had subsided, or were not noticed again, until three months before she was seen by me. A physician again told the parents that the child's heart was weak. I then saw her and sent her to my service for study.

J. S., female, aged three years, admitted to the hospital April 21, 1916.

Family History. Father and mother living and well; one sister, six months old, well.

Past History. Normal delivery; weight at birth eight pounds. No other illness up to the present. Had tonsillitis. Has not had measles.

Present Illness. Patient has had attacks of palpitation on and off for the past three months. The last attack still persists. Patient has no dyspnea; does not cough. No bloody expectoration. When she gets her paroxysmal attacks, patient feels like vomiting, but does so on rare occasions. No gastro-intestinal symptoms; no urinary disturbances. Has no visual or aural disabilities. Appetite poor.

Synopsis: Palpitation on and off for three months.

April 21: Physical examination (a few hours later).

General condition: Good. Patient fairly well-nourished.

Head: Well formed.

Face: Negative.

Eyes: Negative; no petechiæ, palsies, icterus, or nystagmus.

Ears, nose, mastoids: Negative externally.

Mouth: Teeth in good condition. Tongue coated and moist. Throat clear. Tonsils enlarged. No exudate.

Neck: Negative.

Chest: Well formed; expansion fair and equal.

Lungs: Anterior and posterior, negative; no dulness or rales.

Heart: Apex beat not seen or felt; no thrills or abnormal pulsations. Upper border, third rib; right border, right sternal margin; left border, two and a quarter inches from mammillary line. Action regular; fair force; extremely rapid (240 at apex); sounds clear; no murmurs; no accentuations.

Pulses: Equal; regular; rapid.

Abdomen: Lax; tympanitic.

Liver: Upper border sixth space to one-half inch below the costal margin, where edge is distinctly felt.

Spleen and kidneys: Not felt.

Skin: Negative.

Glands: Negative.

Spine: Negative.

Extremities: Upper, negative. No clubbing of fingers or incurving nails.

Extremities: Lower, negative.

Synopsis: Cardiac condition.

May 8: Child in bed, quiet, smiling. Pulse rate 228.

May 8: Electrocardiogram shows a tachycardia of approximately 250 ventricular beats per minute. The *P* waves (auricular) cannot be identified, but are probably combined with the *T* waves, probably falling on the descending limb of the wave.

Heart action is regular, the ventricular complexes during the tachycardia resembling the ventricular complexes taken on April 22, when the heart action was comparatively slow, so that one may assume that the impulses during the paroxysm of tachycardia are supraventricular in origin. It may be safely said that the tachycardia is not ventricular in origin.

May 25. Electrocardiogram taken in an interval in which there was no tachycardia shows a pulse rate of 108 beats per minute. The *P* wave is tall in lead *II*. The *T* wave is inverted in lead *III*. The *P* wave in lead *III* is well marked and upright.

May 26. The record of electrocardiogram is the same except that in lead *III* the *P* wave is so little marked as to be indistinguishable and in certain cycles is diplasic.

Discussion. In this case I saw the child when the cardiac condition was well established and observed the attacks of tachycardia then. The objective symptoms were few; the child would sit up in bed and play with the heart beating at an incredible rate. The attacks were paroxysmal, and in the interval the child, though pale, was not noticeably a sick child. In an attack the child was pale and nervous, but only slightly so; irritable; no swelling of the liver or spleen; no puffiness of the face—simply an indisposition to be disturbed. The child slept well; appetite was good; there were surprisingly few symptoms objectively and subjectively.

Case III.—The third case which I have to report has been under observation for two years in my service at the hospital, having been readmitted twice for his malady. He presents several features in addition to those observed in the other cases which I will try to bring out.

S. P., male, aged ten years, admitted June 16, 1915; discharged August 25, 1915.

Diagnosis. Paroxysmal tachycardia; auricular flutter (on the history).

Chief Complaint. Cardiac palpitation.

Family History. Father and mother living and well. Three brothers and sisters living and well.

Past History. Had measles; no scarlet fever; no sore throats.

Present Illness. Two months ago (?) patient had abdominal pains and vomited often. No cardiac palpitation noted at this time; child did not appear to be weak and played around. Five days ago began to vomit again, at this time cardiac palpitation was noted and the child became very weak and was unable to walk up steps. Bowels constipated.

Examination. General condition fair; moderate cyanosis of lips and ears.

Mouth: Both tonsils contain cheesy follicles, are ulcerated, and contour irregular. Palpable externally.

Nodes: Cervical; axillaries and inguinal nodes palpable.

Skin: Scars on chest and abdomen.

Lungs: Negative.

Heart: Upper border, third rib; right border midsternal line; left border, three-quarter inches to left of midclavicular line. Apex in sixth space.

Pulses: Absolutely irregular periods of tachycardia followed by slow pulse, the beats of which are irregular.

Heart: Action is irregular; first rapid and then slow; sounds of poor quality and valvular in character. No murmurs. Apex beat 200 per minute.

Liver: Sixth rib to one finger below umbilicus. Liver is tender on palpation.

Spleen: Not felt.

Extremities: Knee-jerks present; no edema.

June 29. Heart rate slow, between 70 and 80 per minute. Action irregular in force and rhythm. No murmur heard.

July 1. Marked tachycardia. Apex rate 208. No murmurs heard. Pulse rate difficult to count, small beats being missed about 130. Observed to have continued twelve hours (morning and evening rounds).

July 2. Cardiac rate 100, irregular. Pulse rate 54, very irregular; pulse deficit 46.

Cardiac rate 104, very irregular.

July 5. Tachycardia lasting several minutes observed. Therefore observation of July 1 may indicate constant tachycardia of twelve hours' duration.

August 7. Pulse and ventricular rate equal and regular, 88 per minute. Veins in neck, however, seem to pulsate much more rapidly—too rapidly to be counted. Venous pulsation seems to be rhythmical, now that ventricular action is slow and regular.

August 9. Cardiac rate 104. Pulse rate 100 for two consecutive minutes. Occasional extrasystole present.

August 16. Heart action still slow and moderately irregular.

August 22. Heart action now perfectly regular, about 100 per minute.

Temperature. June 16 to August 25, 98 to 99.2, with occasional rises to 100 or 100.2.

Weight: June 21, 44 pounds 7 ounces; August 22, 50 pounds.

Urinalysis: Usually amber; acid; specific gravity varied from 1012 to 1022, on two occasions there was a faint trace of albumin, microscopically there were white blood cells, and on June 25 there were occasional red blood cells.

Readmitted: September 24, 1915. Patient was discharged from the hospital on August 25, 1915. Felt well until yesterday morning, when he had dyspnea and had slight epigastric pain and vomited. Toward evening his heart began to beat rapidly, causing distress.

Examination: General condition fair; rather marked degree of pallor; respiration increased; somewhat dyspneic.

Eyes: Pupils equal; react to light; no petechiæ.

Mouth: Teeth in bad condition; tongue moist. Tonsils moderately enlarged, irregular in contour.

Glands: Few cervicals; axillaries and inguinal nodes palpable.

Skin: Scar over epigastric region.

Lungs: Negative.

Heart: Action slow; regular; sounds are of good quality; no murmurs; no pulse deficit: no tachycardia. (On admission heart action was very rapid, 190 beats per minute, pulse 130.)

Abdomen: Soft; lax; tympanitic; no fluid.

Liver: Upper border, fifth rib, to one finger's breadth below free border, where edge is indistinctly felt.

Spleen: Not felt.

Genitalia: Negative.

Extremities: Knee-jerks present; no edema.

September 8. Cardiac rate during stage of tachycardia 270 (during last few seconds heart was breaking into slow rhythm). Duration of tachycardia about two minutes regular. Cardiac rate during slow period 104 and irregular.

September 15. Heart action slow and regular. Liver has receded in size to costal margin.

Temperature: September 24 to October 22, irregularly 98 to 100.

Urine: September 24 to October 22, usually amber; acid; specific gravity varied from 1012 to 1024; microscopically occasional white blood cells.

Laboratory Examination: September 20, Wassermann reaction negative.

Readmitted October 2, 1916.

Present Illness. Since leaving hospital two and one-half months ago patient has been at Rockaway Beach. Has had repeated attacks of cardiac palpitation, headache, and nausea, with free intervals of five days to two weeks. Present attack began fifteen days ago.

Synopsis. In Mt. Sinai Hospital, Dr. Koplik's service. Since leaving hospital two and one-half months ago repeated attacks of palpitation and nausea. Present attack, fifteen days' duration.

Physical Examination.

General condition: Good. Patient comfortable, not acutely ill.

Head and neck: Negative.

Mouth: Left tonsil shows small exudate; tonsils slightly enlarged. Teeth in poor condition.

Thorax: Chest well developed. Respiration on both sides free, equal.

Lungs: Resonant throughout; no rales or rubs.

Heart: Action regular; very rapid; sounds clear; no murmurs or thrills. Apex fifth space.

Pulses: Equal; regular; extremely rapid.

Liver: Upper limit sixth rib; lower border not felt below border of ribs.
Abdomen: Rounded; soft; no masses or tender points.
Spleen and kidney: Not felt.
Abdominal reflexes: Present.
Liver: Felt two inches below cubic millimeter.
Extremities: Upper and lower, normal knee-jerks.
Skin and glands: Negative.
Spine and joints: Negative.
Synopsis: Cardiac condition.
October 5. The tachycardia noted on admission has subsided.
November 26. Tachycardia persists.
November 29. Tachycardia has been present for the past twenty-four hours, which is only one of a series which has been continuous for the past few days. Impossible to fix exact duration. Signs of irregularity and premature contractions. Pulse at wrist small but very rapid, 216 at right radial; left radial pulse not so distinct, cannot be counted. Apex 216, 216 at base.
November 29. Tachycardial attack still present. Pulse at wrist 192. Pulsation of jugular of right and left side of neck. Slight puffiness of eyes and brownish color of face. Liver just palpable but not enlarged. Spleen enlarged. Child not uncomfortable.
December 1. Attack still persists. Irregularity present.
December 3. Tachycardial attack has ceased.
December 9. Marked tachycardia this morning.
Urinalysis. Clear; acid; 1014 to 1030; albumin occasionally, very faint trace; microscopically negative.
The electrocardiograms taken in this case are numerous, and may be summarized as follows:
1. A condition of auricular flutter with varying degrees of heart-block 2 to 1 or 3 to 1. There were also ventricular extrasystoles arising from the right ventricle.
2. An auricular tachycardia (auricular tachysystole) which in one cardiogram showed in leads *I* and *II*. Every third auricular beat was blocked and not followed by a ventricular response. In lead *III* the auricular and ventricular beats were equal, the rate of both being 225.
3. An auricular rate of at times 180 to 192 beats with ventricular rate depending on the grade of heart-block 2 to 1 or 3 to 1.

Discussion. This is a case of paroxysmal tachycardia in which the paroxysms may be very short, extending in one actual instance over three minutes and in another over forty-eight hours. In those paroxysms in which the attacks are prolonged it is to be assumed that there may be short periods of rest to the heart which have been interspersed in the prolonged attack. During an attack the rhythm

of the heart is very irregular at times, and there are periods of auricular flutter with heart-block. Between the attacks the rhythm of the heart may be also irregular or show periods of block even when digitalis has not been administered. The duration of the attacks has been referred to. A study of the cardiograms shows that this case is one of auricular tachycardia, as is also the first case. The second case being particularly, according to the cardiogram report, one in which the impulses, during the paroxysm of tachycardia, are supraventricular in origin. A study of the pulse respiration ratio in cases 1, 2, and 3, are given here, with the reservation that the pulse counts were made in a clinical way at the wrist or carotid by nurses in the wards, and must be thus adjudged. As one would expect, *a priori*, the respirations are increased with the pulse rate, but there is nothing objectively approaching what we would name dyspnea. The children did not present the appearance of respiratory distress at any time. To be sure, they were confined to their cribs during the attacks.

PULSE AND RESPIRATION RATIOS. CASE I.

		Respiration.	Pulse.
January	30, 1916	32	124
	31, 1916	28	128
February	1, 1916	28	120
	1, 1916	24	80
	2, 1916	28	76
	2, 1916	44	216
	2, 1916	40	136
	2, 1916	32	120
	2, 1916	28	84
	3, 1916	30	116
	3, 1916	28	96
	4, 1916	32	118
	4, 1916	30	100
	5, 1916	30	96
	5, 1916	28	118
	5, 1916	28	108
	5, 1916	24	88
	6, 1916	28	80
	6, 1916	28	128
February	1, 1917	26	108
	1, 1917	28	180
	2, 1917	26	204
	2, 1917	28	180
	3, 1917	26	128
	3, 1917	28	96
	4, 1917	26	116
	4, 1917	26	120
	5, 1917	26	108
	5, 1917	28	100
	5, 1917	26	104

PULSE AND RESPIRATION RATIOS. CASE II

		Respiration.	Pulse.
April	21, 1916	28	156
	21, 1916	36	140
	22, 1916	36	108
	27, 1916	26	92
May	1, 1916	28	100
	4, 1916	24	70
	8, 1916	24	228
	9, 1916	24	78
	11, 1916	36	200
	11, 1916	26	240
	17, 1916	36	200
	17, 1916	28	192
	20, 1916	40	108
	22, 1916	28	208
	25, 1916	24	92
	26, 1916	24	120
	27, 1916	36	212
	30, 1916	24	96
June	1, 1916	20	92
	4, 1916	20	80
	6, 1916	36	92
	7, 1916	36	250
	8, 1916	44	205
	8, 1916	32	160
	9, 1916	28	112
	10, 1916	36	200
	11, 1916	38	248
	12, 1916	28	100
	13, 1916	20	88
	14, 1916	28	110
	14, 1916	26	84
	15, 1916	26	84
	16, 1916	20	104
	17, 1916	32	128
	18, 1916	24	100
	20, 1916	20	84
	21, 1916	24	96
	22, 1916	24	120

PULSE AND RESPIRATION RATIOS. CASE III

			Respiration.	Pulse.
June	16 to June	22, 1915	30	160
	16 to	22, 1915	24	96
	23 to	29, 1915	24	92
	23 to	29, 1915	24	76
	30 to July	6, 1915	24	94
	30 to	6, 1915	24	80
July	7 to	13, 1915	28	96
	7 to	13, 1915	24	80
	14 to	20, 1915	24	100
	14 to	20, 1915	24	80
	21 to	27, 1915	24	102
	21 to	27, 1915	24	80

PULSE AND RESPIRATION RATIOS. CASE III (continued).

		Respiration.	Pulse.
July	28 to August 3, 1915	24	154
	28 to 3, 1915	24	80
August	4 to 10, 1915	24	104
	4 to 10, 1915	20	80
	11 to 17, 1915	24	96
	11 to 17, 1915	22	88
	18 to 24, 1915	28	112
	18 to 24, 1915	22	88
September	4, 1916	34	144
	10, 1916	30	136
	17, 1916	28	100
	24, 1916	24	96
	28, 1916	24	108
October	4, 1916	24	56
	15, 1916	24	88
	31, 1916	24	84
November	10, 1916	24	162 (?), 176 (?)
	12, 1916	24	80, 120, 110
	15, 1916	24	108, 64
	26, 1916	24	90
	29, 1916	24	162, 196, 88
December	5, 1916	24	60
	10, 1916	24	104
	12, 1916	24	112
	17, 1916	24	72
	26, 1916	24	54
January	6, 1917	24	72, 80, 90
	14, 1917	24	70
February	11, 1917	24	90
	16, 1917	24	84
	19, 1917	24	88
March	2, 1917	20	72
	9, 1917	24	104
	11, 1917	44	160
	14, 1917	20	104
	17, 1917	22	80
	19, 1917	24	112
	19, 1917	20	84
	30, 1917	28	120
April	1, 1917	24	104

APRIL 5, 1917. A PAROXYSM, TACHYCARDIA

		Respiration.	Pulse.
2.45 P.M.	Attack started	144	32
3.00 P.M.		208	44
3.15 P.M.		196	40
3.30 P.M.		200	40
3.45 P.M.		192	38
4.00 P.M.		200	40
4.15 P.M.		204	42
4.20 P.M.		100	(a pause) 26
4.30 P.M.		180	40
5.00 P.M.		184	38
5.30 P.M.		192	40
6.00 P.M.		188	38
6.30 P.M.		180	36
7.00 P.M.		184	30

APRIL 8, 1917

		Respiration.	Pulse.
10.00 A.M.	Attack started	200	40
10.30 A.M.	.....	180	40
11.00 A.M.	.....	192	38
11.30 A.M.	.....	196	38
12.00 M.	Pulse intermittent	188	36
12.30 P M.	.....	192	36
1.00 P.M.	.....	196	38
1.30 P.M.	.....	192	36
2.00 P.M.	.....	196	36
2.30 P.M.	.....	196	36
3.00 P.M.	.....	180	32
3.30 P.M.	.....	176	32
4.00 P.M.	.....	168	30
4.30 P.M.	.....	164	28
5.00 P.M.	.....	164	28
5.30 P.M.	.....	150	28
6.00 P.M.	Pulse intermittent	150	28
6.30 P.M.	.....	130	26
7.00 P.M.	.....	130	26
7.30 P.M.	Attack ceased	120	28
9.00 P.M.	.....	96	24
11.00 P.M.	.....	96	26
12.00 MID.	.....	100	24
12.30 A.M.	.....	104	24
1.00 A.M.	.....	104	24

Additional studies of the pulse and respiration ratios in Case III, showing the occurrence of short paroxysms of tachycardia and duration of paroxysms.

APRIL 13, 1917

Time.	Pulse Radial.	Apex.	Notes.	Respiration.
12.30 A.M.	80	..	Attack started; intermittent.	24
1.15 A.M.	56	..	Irregular, of fair quality, at first feeling rapid and fluttering, and suddenly dropped to perceptible amount of 56.	24
1.35 A.M.	56	..	.....	24
2.00 A.M.	?	?	Fluttering.	24
2.30 A.M.	104?	..	.....	24
3.00 A.M.	80	104	.....	24
3.30 A.M.	92	..	.....	24
4.00 A.M.	76	?	Very irregular.	24
5.00 A.M.	88	120	Radicle irregular; apex bounding.	24
5.30 A.M.	?	160	.....	24
6.00 A.M.	?	200	Complains of sticking pain in left axilla.	22
6.30 A.M.	?	136	Respirations abdominal and seem restrained on patient's part.	24
7.00 A.M.	?	200	.....	24
7.30 A.M.	?	204	.....	26
8.00 A.M.	?	196	.....	26
8.30 A.M.	?	196	.....	24
9.00 A.M.	?	192	.....	24

APRIL 13, 1917 (continued).

Time.	Pulse Radial.	Apex.	Notes.	Respiration.
9.30 A.M.	?	196	.....	24
10.00 A.M.	?	192	.....	24
10.30 A.M.	?	180	.....	24
11.00 A.M.	..	176	.....	24
11.30 A.M.	?	?	.....	24
12.00 NOON	..	152	.....	24
1.00 P.M.	..	168	.....	24
2.00 P.M.	..	168	.....	24
2.30 P.M.	..	172	.....	22
3.00 P.M.	..	170	.....	24
4.00 P.M.	..	160	.....	24
4.30 P.M.	..	164	.....	22
5.00 P.M.	..	172	.....	24
5.30 P.M.	..	176	Attack still on; pulse imperceptible at times; patient has headaches and complains of pain in left axilla occasionally.	24
6.00 P.M.	..	180	.....	26
6.30 P.M.	..	172	.....	24
7.00 P.M.	..	176	.....	24
7.50 P.M.	88	88	Intermittent.	24
7.55 P.M.	128	..	.....	24
8.30 P.M.	..	188	.....	24
9.00 P.M.	116	..	Pulse varied, 88 to 188; respirations 24.	24
10.00 P.M.	96	..	Distinctly tricotic at 188.	24
11.00 P.M.	120	..	.....	24
12.00 MID.	..	144	.....	24

Pulse and respiration ratio and short momentary tachycardial paroxysms in the intervals of prolonged paroxysms.

CASE III. APRIL 14, 1917

Time.	Pulse Radial.	Apex.	Notes.	Respiration
1.00 A.M.	88	..	.....	24
2.00 A.M.	..	144	.....	28
3.00 A.M.	..	160	.....	24
4.00 A.M.	..	120	.....	24
5.00 A.M.	80	..	.....	24
6.00 A.M.	136	..	.....	24
7.00 A.M.	48	140	.....	24
7.30 A.M.	..	188	.....	24
8.00 A.M.	..	184	.....	24
8.30 A.M.	..	?	.....	24
9.00 A.M.	..	180	.....	24
9.30 A.M.	..	172	.....	24
10.00 A.M.	..	160	.....	22
1.00 P.M.	..	186	.....	24
1.30 P.M.	..	192	.....	22
2.00 P.M.	..	200	.....	26
2.30 P.M.	..	184	.....	24
3.00 P.M.	..	180	.....	24

CASE III. APRIL 14, 1917 (continued).

Time.	Pulse Radial.	Apex.	Notes.	Respiration.
4.30 P.M.	..	156	.....	22
5.00 P.M.	..	160	.....	22
5.30 P.M.	..	164		
6.00 P.M.	..	136	Pulse varying, 200 to 136, irregular and intermittent at times; complains of headache.	24
6.30 P.M.	..	136	.....	24
7.00 P.M.	..	156	.....	24
8.00 P.M.	84	..	.....	22
9.00 P.M.	72	..	.....	24
10.00 P.M.	80	..	Attack ceased.	24
11.00 P.M.	80	..	.....	24
12.00 MID.	80	..	.....	24
1.00 A.M.	80	..	April 15, 1917.	24
2.00 A.M.	80	..	.....	24
3.00 A.M.	84	..	Attack lasting two minutes; pulse 184; respirations 24.	24
4.00 A.M.	80	..	.....	24
5.00 A.M.	80	..	.....	24
6.00 A.M.	84	..	Attack of rapid pulse, approximately lasting thirty seconds.	24
7.00 A.M.	80	..	.....	24
9.00 A.M.	84	..	.....	22
11.00 A.M.	108	..	.....	22
1.00 P.M.	160	..	.....	22
3.00 P.M.	120	..	Attack lasting two minutes; pulse suddenly became very rapid, 204 (?), then heart-block about three seconds, then 88 regular.	22
5.00 P.M.	108	..	.....	22
7.00 P.M.	106	..	.....	22
9.00 P.M.	96	..	.....	22
11.00 P.M.	84	..	.....	24

Several questions arise in connection with these cases which are of interest. The first question asked me by physicians is, What is the fate of these cases? We have no records of any cases which have been followed from childhood to adult life. We cannot say, therefore, whether the abnormal condition of the heart innervation leads ultimately to exhaustion of the heart muscle with all the symptoms of heart weakness, decompensation and ultimate death. This must remain for future observation. It may be that many of these children being attacked by some intercurrent affection die of heart weakness and never reach adult life. The opposite may be true that the heart may ultimately return to its normal innervation and no signs of the previous affection may be left. Another point of interest is the management of these cases. They all seem to be perfectly comfort-

able, if not subjecting the heart to any excessive strain, such as muscular exertion in play or running. It would seem in this that our observations agree with a solitary case in the literature published by Hutchinson and Parkinson of tachycardia in a child, aged two years and eight months. In this case the subjective and objective symptoms were few and resembled closely those of Case I in our series. Digitalis temporarily controls but does not cure the condition; on the contrary it is difficult to prevent a digitalis heart-block if digitalis is administered, and it would seem as though the children were as well off without digitalis as with the drug. On the other hand, in a case (as in my Case I) in which the heart threatened to collapse in the first attack of tachycardia, digitalis would seem to have saved the day. In this case the heart is now very intolerant of the use of digitalis, which, if administered incautiously even in small doses, is apt to bring about a reduction of pulse rate with heart-block which is disagreeably alarming. So that we may infer that the heart is peculiarly sensitive in these cases to the action of the drug, which must be used in controlling ordinary attacks with extreme caution. The constant use of digitalis in these children is to be rejected. It is to be used in the paroxysms and in cases only of imminent cardiac failure and collapse.

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GRAPHIC RECORDS OF REFLEXES AND CLONUS[1]

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AND

L. G. ROWNTREE, M.D.

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(From the Department of Medicine, University of Minnesota)

The need of exact and permanent records of tremors,[2] reflexes and clonus is beyond question. Hitherto the physician has been compelled to be content with memory pictures. Obviously, this is unsatisfactory.

It was with the idea of meeting a glaring need that an attempt was made to devise methods of graphically recording these phenomena. The credit for the mechanical devices utilized is due to Dr. Morris.

Two great problems are encountered: (1) methods of record, and (2) interpretation of records. Our efforts up to date have centered on the former. In the beginning it was difficult to secure consistent records, but, after a year's experience, various difficulties have been met, one after another, until at present we feel confident that we can secure consistent records of reflexes. At present we are considering their interpretation and are meeting with some degree of success. However, as many of the records are relatively complex the question of interpretation will be deferred and will be the subject of further investigation and of future publication.

[1] Since writing this paper, the attention of the authors has been called to an article by A. Bornstein and A. Saenger in the Deutches Zeitschrift f. Nervenheilkunde, Bd. lii, 1, 2 Heft, entitled "Untersuchungen über den Tremor und andere pathologische Bewegungsformen mittelst des Saitengalvanometers," in which work somewhat similar to ours is reported.—L. G. R.

[2] The Tremograph, devised by Dr. Morris, has been already described in the Journal Lancet, 1917, xxvii, 423.

Concerning reflexes there is much unknown that is fundamental in nature. As already intimated, we will not enter into a discussion of these matters in this paper but will confine our attention purely to the question of methods of obtaining and to the demonstration of records.[1]

The electrocardiograph apparatus of the Taylor Cambridge type has been utilized and modifications have been made to meet our particular problems.

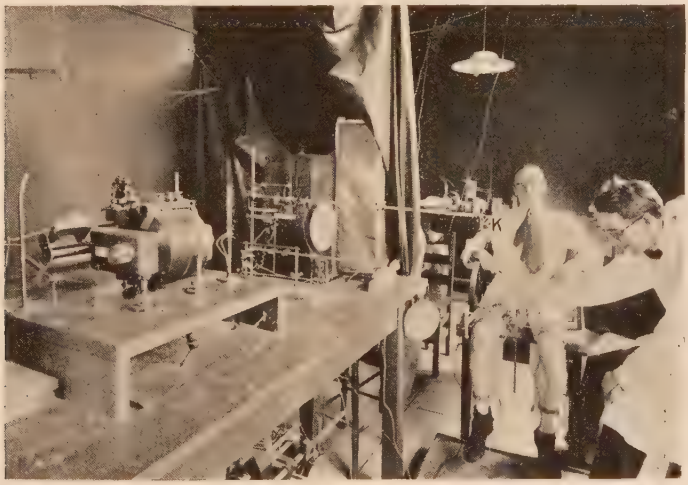

FIG. 1.—Shows the apparatus in use, the patient in position, and the operator at work.

In securing records of knee-jerks, the patient is seated in a specially devised chair upon an electrode molded to the form of the gluteal region. The chair is sufficiently high from the ground to permit the feet to swing free. Mechanical leg attachments, in the form of laterally adjustable swing boards, are hinged to the front edge of the chair. These are adjusted to the patient's legs and secured to them by means of straps. Electrodes are attached, but only one at a time is connected with the string galvanometer. Preliminary study is made and the point yielding maximum resistance

[1] A more detailed account of this work has been presented by Dr. Morris as his thesis for the Sc.D. degree.

is marked. This constitutes the invariable point of contact in eliciting the reflexes. An insulated contact, and a small wire net

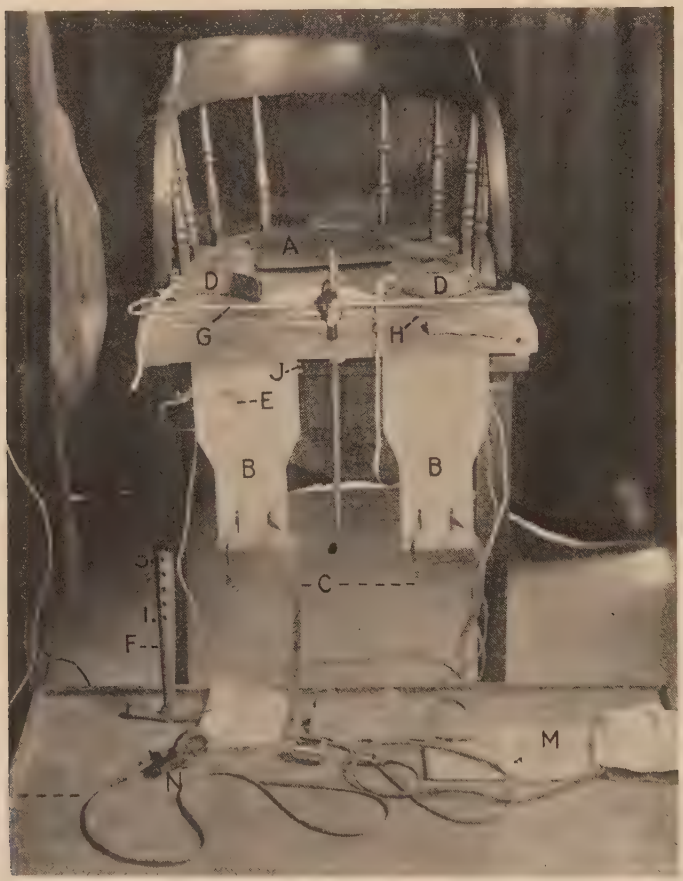

FIG. 2.—The chair and its attachments, electrodes, hammer used in obtaining reflexes; and arm band of blood-pressure apparatus, and indicator used in obtaining graphic records of clonus. *A*, electrode molded to the form of the gluteal region; *B, B*, swing boards; *C*, straps; *D, D*, electrodes for leg attachment; *E*, wire net for electrical contact with (*F*) hammer; *F*, hammer; *G*, horizontal bar; *H*, second horizontal bar; *J*, eyelets; *K*, pulley (shown in Fig. 1); *L*, aperture before lens (shown in Fig. 1); *M*, air bag; *N*, Marey tambour.

attached by adjustable supports to the swing board, is placed over the area already marked. The hammer which produces an electric

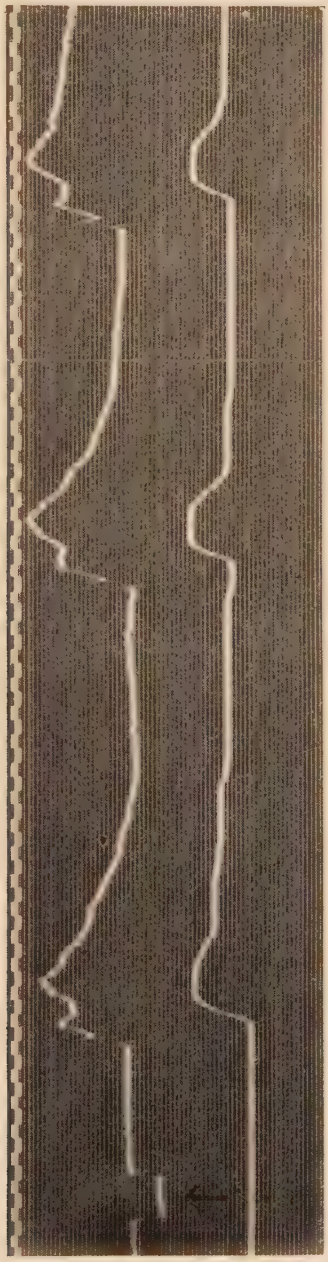

FIG. 3.—Picture of three knee-kicks, same individual, showing how exactly the picture can be reproduced. The arrow indicates the effect of introduction of 1 millivolt.

contact resulting in a fling in the signal magnet, is adjusted to the horizontal bar so that it strikes directly in the desired spot on either leg. Along the handle of the hammer there are five holes. The

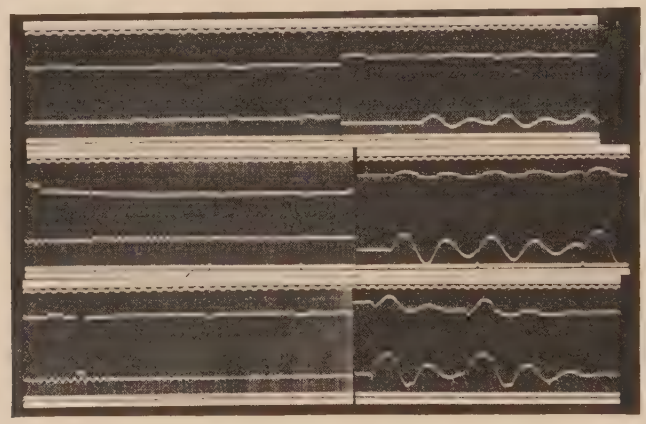

FIG. 4.—The effect of reinforcement on sluggish reflexes. To left are shown three reflexes difficult to elicit: the right, the same under reinforcement (reduced).

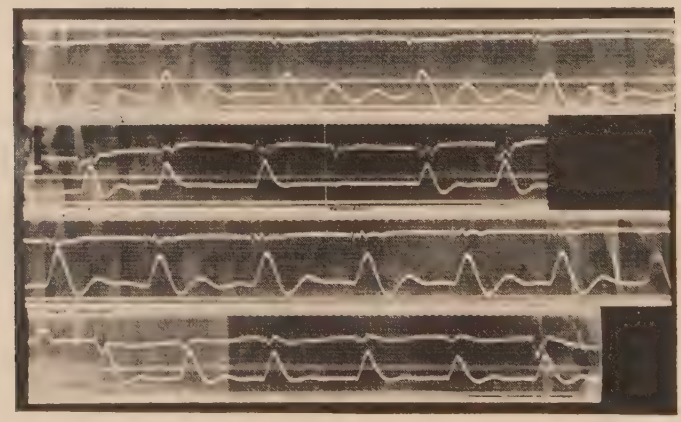

FIG. 5.—Tracings 1 and 3 show left and right knee-kick respectively: tracings 2 and 4 the same reinforced (reduced).

hammer is usually secured on the horizontal bar through hole (1), thereby furnishing the lightest stroke possible with this apparatus. The second lighter horizontal set-bar is so placed that the hammer

may be dropped from any desired angle. Ordinarily, however, 90 degrees is the one advised. In the other edge of the swing board are inserted three eyelets, to one of which is attached a hook which is secured to an inelastic cord which runs over an adjustable frictionless pulley to a hanging indicator suspended in front of the aperture in front of the lens of the electrocardiograph. The indicator produces a shadow parallel to that of the string galvanometer. Holding the indicator in position on the other side is a coiled steel spring, the tension of which is adjustable. So long as the indicator remains

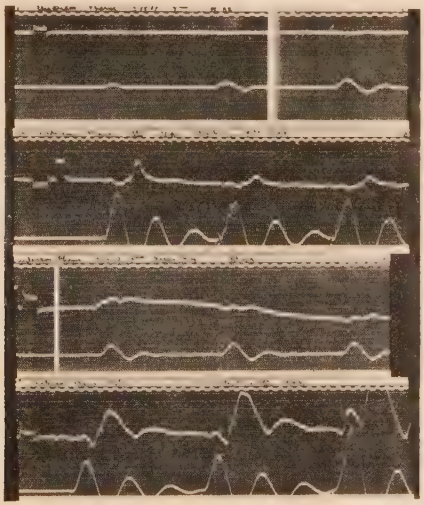

FIG. 6.—Effect of strychnin. Tracings 1 and 3 show sluggish reflexes: 2 and 4 the same reflexes forty-five minutes after administration of $\frac{1}{10}$ grain of strychnin (reduced).

in a vertical position the tension on the string leading to the swing board is constant. A time-marker[1] indicating one-tenth of a second has been used in most of the work.

In these pictures the upper tracing represents the time-marker, one-tenth of a second being indicated. The second record represents the electrical response, the picture resulting from the shadow of the galvanometer string. The third record represents the mechanical

[1] A tuning-fork yielding $\frac{1}{100}$ of a second has been used in a few instances but has not proved entirely satisfactory.

response as pictured by the movement of the indicator; and the fourth depicts the instant of contact. In many of the records

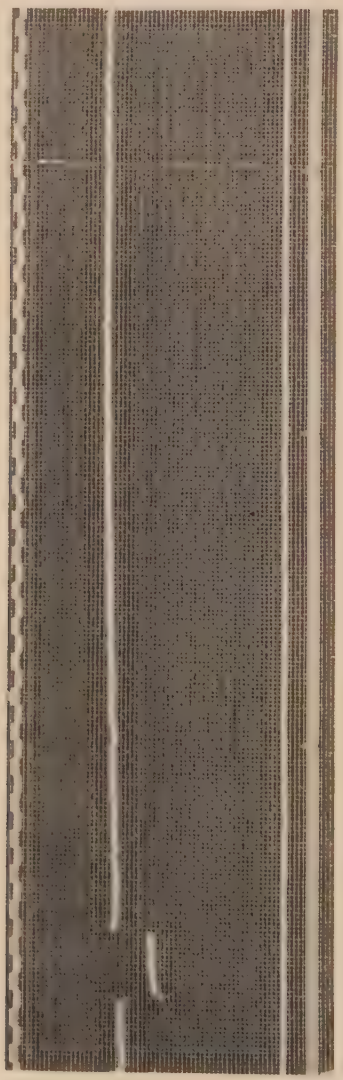

Fig. 7.—Tracings of right and left knee-kick in tabes dorsalis: actual size.

the deflection resulting from the introduction of a millivolt is shown just prior to the reflex. This indicates the tension of the string.

Clonus Records. In securing records of clonus, the electrocardiographic apparatus is also used as above, substituting a special device for recording the mechanical movement. A Marey tambour with a long indicator is used. This is connected by rubber tubing

Fig. 8.—Knee-kick in case of multiple sclerosis; natural size.

to an air-bag of a blood-pressure apparatus which is placed in a suitable position about the extremity from which the record is to be taken. The bag is slightly inflated, the clonus is elicited and the record taken in the ordinary manner.

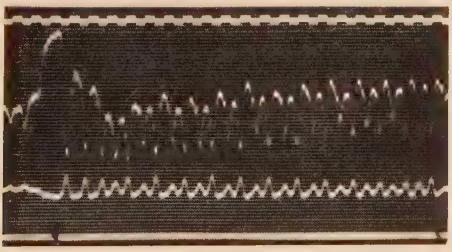

Fig. 9.—Ankle-clonus showing alternation.

A definite start has been made in the recording of reflexes and clonus. Records from 300 individuals have been taken. Experimental work bearing on their interpretation is now in progress. Future publications dealing with interpretation and presenting records of these phenomena in various diseases is contemplated.

THE NERVOUS SYMPTOMS OF POLYCYTHEMIA VERA[1]

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It seems worth while to emphasize the nervous symptoms presented by patients with polycythemia vera, not because the case reports and various studies of this condition fail to make mention of their frequent occurrence, but because a failure to keep them in mind very often has led to diagnostic mistakes, and in some instances to cerebral operations, with the idea that the symptoms were the result of brain tumor.

If you have in mind the very striking appearance of some patients of this group with their marked cyanosis or, probably better, reddish cyanosis it would seem as if this disease would be recognized promptly; but alas, how often do we fail to see what is just in front of our eyes because with vision is not combined thinking, and the application of experience acquired by previous observation and reading. Then, too, sometimes patients with polycythemia vera are neither abnormally blue nor red. In fact, occasionally they may be pale. As Osler pointed out in his paper on "Erythremia or Polycythemia with Cyanosis," in 1908,[1] there may be much variation in the color of people, depending on the condition of the cutaneous vessels and the rate of blood flow. If the capillaries are full and the flow slow cyanosis predominates; if the current is rapid an arterial color is prominent. In polycythemia usually there is a definite mingling of the two colors, resulting in what might be termed a red cyanosis. These variations are strikingly evident if

[1] Osler: Lancet, 1908, i, 143.

the changes produced by warmth or cold or by changes in position of an extremity are noted in the same patient. What is particularly important from the point of view of diagnosis is that the skin in patients with polycythemia sometimes may show pallor due presumably to vasoconstriction or peripheral circulatory failure, and in these cases the diagnosis is likely to be missed unless a blood count or the finding of an enlarged spleen point the way.

The nervous symptoms are various. Vaquez's[1] original case had vertigo, buzzing and whistling in the ears and paroxysms of dizziness. In Osler's report[2] which aroused interest in the subject and which in America and England has been in large part responsible for the general recognition of this condition as a disease entity, he describes 4 cases which he himself observed and collects 5 others from the literature. Of these 9 case reports all except 1 contain mention of nervous symptoms such as vertigo, fulness in the head, headache, pain and prickling sensations in the extremities, ringing in the ears, loss of consciousness, thickness of speech, staggering gait, muscle weakness, blurring of vision, etc. Senator,[3] in his excellent little monograph *Polyzythämie and Plethora*, begins his description of symptomatology, etc., by saying that subjective symptoms usually occur, due to the overfilling of the bloodvessels and the abnormal composition of the blood, such as giddiness, rush of blood to the head, flashes of light, migraine-like attacks of pain in the head, etc.

A brief resumé of 10 cases of polycythemia which I have had opportunity to study on my services at the Carney and Peter Bent Brigham Hospital, or that of my colleague, Dr. Cushing, on the surgical service at the Peter Bent Brigham Hospital, will serve to illustrate the frequency and importance of nervous symptoms in these patients.

Case I.—Female, aged fifty-one years, admitted to the medical service of the Carney Hospital March 15, 1911. Nervous symptoms were frequent headaches; sharp, shooting pains through the head, face, and back of neck; attacks of transient blindness; at other times blurring of vision.

[1] Compt. rend. Soc. de biol., 1892, p. 384.
[2] Am. Jour. Med. Sc., 1903, cxxvi, 187.
[3] Senator: Verlag v. August Hirschwald, Berlin, 1911.

Many of these symptoms were present for eight years before admission, during which time her red blood count ranged between 7,512,000 and 10,616,000. Her color was usually cyanotic. She came to the Carney Hospital with abdominal symptoms. At this time the only deepening of color noted was a slight cyanosis of the fingers, though her red blood count was 8,500,000. She died two days after admission, and autopsy showed thrombosis of the portal vein and its branches; infarction of the small and part of the large intestine; splenomegaly. Permission to examine the brain could not be obtained.

Case II.—Male, aged fifty-five years, admitted to the medical service of the Carney Hospital April 18, 1911. No nervous symptoms of a definite nature. No cyanosis or erythema noted. Red blood counts: highest 8,224,000, lowest 6,752,000.

Case III.—Female, aged forty-five years, first came to the medical outdoor department of the Peter Bent Brigham Hospital April 26, 1915. Her nervous symptoms were dizziness, faintness, nervousness, difficulty in sleeping, and disturbance of vision, although repeated eye examinations have shown no visual defect. Her color was a reddish, cyanosis or congestion, particularly evident in face and neck. Her hemoglobin ranged between 107 per cent. and 112 per cent., and her red blood count between 5,270,000 and 5,620,000.

Case IV.—Male, aged fifty-five years, admitted to the surgical service of the Peter Bent Brigham Hospital September 29, 1915. Nervous symptoms were recurring headaches of twenty years' duration; for ten years eye symptoms, consisting of fatigue and poor vision, scintillating scotomata, and blind spots in his fields of vision; for six years recurring sensations of tingling in the left arm and leg to which, in June, 1915, was added transitory weakness of the left arm, causing a wrist-drop, and in August, 1915, sudden complete paralysis of the left arm, which lasted for twenty-four hours. Ten days before admission he began to have severe headache and paresthesia of the left side of his body. Then his left arm became weak, so that four days ago he carried it in a sling and was unable to use his fingers or move his wrist. At this time the muscles in his left arm occasionally twitched and contracted. Three days ago the left side of his face became weak and weakness of the left arm muscles progressed to practically complete loss of motion. Two days ago the left leg became weak; speech gradually became difficult. For a week there has been marked photophobia. On examination after admission there were found slight cyanosis of lips, fingers, ears, and mucous membranes of mouth, and later an increased reddish color rather than a definite cyanosis was noted; tender point over the vertex of the head; paralysis of the left face and arm; paresis of the left leg; hypesthesia of the left arm and leg; left astereognosis; tendency to conjugate deviation of the eyes to the right and restriction of conjugate movements to the left; deep reflexes of left arm greater than

right; positive Babinski sign on left; left homonymous hemianopsia; edema and hyperemia of optic disks. His hemoglobin was 180 per cent. and red blood count 6,960,000. He had a cerebral decompression and subsequently died. Autopsy showed bilateral thrombosis of the cerebral arteries with areas of cortical degeneration in both cerebri; mural thrombosis of the aorta; thrombosis of the coronary arteries; infarcts in the heart and spleen; splenomegaly.

Case V.—Male, aged sixty-three years, admitted to the medical service of the Peter Bent Brigham Hospital August 16, 1915. The nervous symptoms were transitory dizzy spells for one year; toe-drop for three months; for a few months memory had been failing; three days before admission he noticed numbness of fingers of left hand and increasing weakness of left arm, so that by noon it was paralyzed; a little later in this day weakness began in his left leg and increased to paralysis the day of his admission. On admission there was some weakness evident on motion of eyes to left; paralysis of left arm and leg with decreased reflexes; optic disks showed slight blurring. The color of the face was reddish and the lips showed a deep red-blue color. The patient remained in this general condition for two months with a hemoglobin of 182 per cent. to 206 per cent. and red blood count of 8,944,000 to 9,320,000. He then gradually went to pieces and died. Autopsy showed thrombosis of the cerebral artery, with areas of softening in the right cerebral cortex; thrombosis of the left renal, pulmonary and splenic arteries and of the right renal vein and the inferior vena cava; infarcts of the lung and spleen; slight splenomegaly.

Case VI.—Female, aged fifty-four years, admitted to the medical service of the Peter Bent Brigham Hospital March 20, 1916, and readmitted December 6, 1916. The nervous symptoms were dizziness of about fourteen months' duration, and for ten months occurring almost daily; for ten years she has been seeing black spots before here eyes moving laterally (ophthalmoscopic examination shows numerous opacities of vitreous); for some time she has had periods of feeling dazed and of other queer sensations; once while walking to the bath room it seemed as if she were trying to walk on air, and she raised her legs high like a horse; six months ago her right leg lost its power and felt dead for five minutes; she has had periods of peculiar numbness of her lips and tongue. Her color was increased and of a reddish cyanotic type, and her hemoglobin was 164 per cent. and red blood count 7,380,000. For eight months after leaving the hospital she continued to have recurrent headache, trouble in vision, and nervousness. Then eight days ago she had numbness of the entire right half of her body; she could move her arm and leg but could not feel them move, though she saw that they were moving. These attacks recurred several times during the eight days, and she had difficulty in walking, staggering like a drunken man. These attacks were followed by pins and needles sensations. She has had flashes of light before her

eyes and scintillating scotomata always seen to the right. On her readmission physical examination showed slightly decreased sensations of temperature, pain, pressure, and touch on the right side of the face and right arm and leg. No signs of ataxia could be made out in the legs, but there was slight difficulty in finger-to-finger and finger-to-nose tests, apparently due to difficulty in telling where the right hand was. Her hemoglobin was 122 per cent. and red blood count 6,696,000.

Case VII.—Male, aged fifty years, first came to the medical outdoor department of the Peter Bent Brigham Hospital August 4, 1916. The nervous symptoms were occasional headache and slight dizziness almost daily. His hemoglobin was 120 per cent. and red blood count 8,400,000. The note on his color was "looks pale in spite of high hemoglobin."

Case VIII.—Male, aged fifty-six years, admitted to the surgical service of the Peter Bent Brigham Hospital November 22, 1916. The nervous symptoms were decreasing vision for two or three months and for ten days slightly blurred vision and diplopia; three weeks ago he felt dizzy and staggered to the right side on several occasions; about the same time his feet began to feel numb and he would catch them on the stairs; his gait became shuffling, more on left; for one week was unable to walk or to move his left leg; for two weeks had almost constant headache. On physical examination his mucous membranes were pale; there was palsy of the left arm and leg; partial paralysis of the left face; positive Babinski sign on the left; absent knee-jerks on the left. The patient gradually grew more drowsy and stuporous. On November 25 cerebral decompression was done. Subsequently blood examination showed hemoglobin of 150 per cent. and a red blood count of 9,200,000. The patient died November 29 and autopsy showed sclerosis of the cerebral arteries and cerebral softening; the spleen was small; no thromboses of vessels were found.

Case IX.—Male, aged fifty years, admitted to the surgical service of the Peter Bent Brigham Hospital November 26, 1916. The nervous symptoms were slight frontal headache of three or four weeks' duration; difficulty of speech for one week, increasing in four days to inability to say more than "yes" and "no;" blurred vision for three days; paralysis of the right arm for twenty-four hours and the right leg for six hours. Physical examination showed paralysis of the left external rectus muscle of the eye; right trigeminus anesthesia; right facial paralysis; paralysis of the right palate and right trapezius muscle; right hypoglossal paralysis; paralysis of the right arm and leg; right hemianesthesia; positive Babinski sign on right and right ankle-clonus. The color does not appear to have been abnormal, as in two notes in regard to the skin no mention is made of any abnormality of color, though the blood examination showed during twelve days three observations of hemoglobin of 137 per cent., 140 per cent., and 135 per cent. and red blood counts of 6,800,000, 6,728,000, and 7,040,000 respectively.

Case X.—Female, aged fifty-six years, admitted to the medical service of the Peter Bent Brigham Hospital January 4, 1917, and readmitted April 21, 1917. The nervous symptoms were at first slight fulness in the head. Later there was very slight headache, numbness in one side of the face, and attacks of weakness, in which, as she says, "she feels as though she was sinking down," but these symptoms were very slight and possibly were the result of suggestion. There were no eye symptoms beyond slight fatigue and occasional blurring. The symptom that brought her to the hospital was gastric discomfort.

Her color, especially of her face and neck, was the characteristic red, cyanotic type. Blood examinations showed a variation between 128 per cent. and 155 per cent. of hemoglobin and a red blood count between 5,440,000 and 7,790,000.

Of these 10 cases which I have observed all but 2 (Cases II and X) showed very definite nervous symptoms, and in most the nervous disturbances were the chief cause of the patient's discomfort. These symptoms varied in duration from a few days to many years. The most frequent symptoms were headache and dizziness. Other common symptoms were disturbances of vision such as easily induced fatigue of the eyes, blurring of vision, scotomata often scintillating, transient blindness, hemianopsia, and diplopia. Disturbances of sensation, particularly paresthesia, occurred. In several patients motor disturbances, such as paresis and paralysis, were seen. The case in which these were transient and recurred is of special interest. The nervous symptoms in some of the patients were sufficiently focal in character to lead to the diagnosis of brain tumor. Case IV was of special interest in this connection, for during a period of ten years, during which he was seen repeatedly by ophthalmologists and neurologists, brain tumor often was suggested as the cause of his symptoms, and no one seems to have suspicioned the polycythemia until he was admitted to the hospital, and even when the blood count was known it was still thought possible that some of the focal symptoms were due to a cerebral tumor.

Ascher[1] in a study of the eye changes in several patients with polycythemia notes a slight swelling of the optic disk which he thinks might be due either to the polycythemic congestion or to

[1] Klin. Monatsbl. f. Augenb., 1914, liii, 388.

slight edema. He emphasizes asthenopia as a frequent symptom in patients without refractive errors. Two of our patients gave this symptom and told of repeated but fruitless efforts to get suitable adjustment of glasses.

What is the cause of the nervous symptoms? In many of the cases undoubtedly the cause lies within the central nervous system. The contents of my consultation slip on Case IV bears on this, and I quote it in part: "The cerebral symptoms and peripheral effects might be explained as of focal origin; cerebral thromboses and hemorrhage. Both occur in reported cases. In the absence of other pressure phenomena in this case and the history of onset of paralyses, I believe there is stronger probability of cerebral vascular disturbance—at first general and slight, simply disturbance in the venous channels with poor circulatory nutrition, later focal and more marked, thrombotic or hemorrhagic—than of cerebral neoplasm. If the latter, it is a slowly developing type; if the former, the polycythemic condition would be the primary cause. My personal feeling is that polycythemia with secondary vascular circulatory disturbance is the probable diagnosis." In this patient and in Case V vascular thromboses were found at autopsy to explain at least the recent cerebral symptoms. These thromboses might be said to arise in part from diseased conditions in the vessel wall and in part from the changed condition of the blood. Less marked nervous symptoms, on the other hand, must be due to temporary circulatory disturbances especially where they are so transitory. That more definite organic cerebral lesions may occur without evident thrombosis or lesion in the vessel wall is shown by Case VII where with areas of cerebral softening no thrombi and almost no vascular lesion were found at autopsy. A case in every way similar to this was reported by Goldstein[1] with focal softenings in the brain and cerebral vessels free of lesions.

In this group of cases the color of the skin was very interesting. In Case I, when seen after the development of abdominal symptoms due to mesenteric thrombosis, very little cyanosis was noted, though this patient had shown the typical color during previous observa-

[1] Med. Klinik, 1910, vi, 1492.

tions. In Case II no cyanosis or erythema was noted. In Case VII the note was made that the patient "looks pale in spite of the high hemoglobin." In Case VIII cutaneous pallor was noted and the increased hemoglobin and high blood count were not discovered until after cerebral operation. In Case IX the color does not appear to have been abnormal. In Cases III, IV, V, VI, and X there was typical cyanosis or erythema. Thus of 10 cases $\frac{1}{2}$ (5) at the time of hospital observation failed to show color in the skin that would suggest the diagnosis of polycythemia.

A striking thing in this group was the similar age at the time of admission to the Hospital 51, 55, 45, 55, 63, 54, 50, 56, 50, and 55 respectively. Though this may be mere coincidence it is rare to get so little age variation in a group of patients with a single diagnosis. From the history given by these patients it is suggested that often the blood condition exists prior to very definite symptoms of any sort and the development of symptoms may occupy a long time. We have very little data on which to base an opinion as to the probable average age of development of polycythemia. We know from observations of high blood counts among members of families of patients with polycythemia, who have symptoms that the condition exists without symptoms so presumably it develops often long before symptoms occur.

Summary. Nervous symptoms are very frequent in polycythemia vera, and usually they are the symptoms that lead the patient to seek medical advice. Since quite often polycythemic patients fail to show cyanosis or erythema with these nervous symptoms, other cerebral lesions such as brain tumor are suspected. In the earlier stages such symptoms must result from simple circulatory disturbances; in the later stages cerebral softening or cerebral hemorrhage and local vascular lesions such as thrombosis are often found.

DISCUSSION

Dr. Sailer had had under his care a patient with a typical case of polycythemia with splenomegaly, who complained of headache, nausea and

vertigo, another patient complained of intense pain in the pelvic girdle without demonstrable disease of the bones; injections into the sciatic nerve gave no relief. The same syndrome developed in a case of Banti's disease after splenectomy had been performed.

The first patient died apparently from exhaustion, while the second patient recovered.

Dr. Christian (closing) said quite a number of these patients had had the experience of going repeatedly for examination of the eyes; the ophthalmologist had fitted them with glasses on the basis of a very slight astigmatism, or a very slight disturbance in the vision; and the result had been very unsatisfactory. The eye symptom most common in such cases is fatigue, very quickly coming on. Ascher in one of the ophthalmological journals has described this as a rather characteristic symptom of polycythemia and one which, from the point of view of the eye examination, should suggest the possibility of this disease. As this writer explains it, the weakness involving the eye muscles is due to the fact that these muscles are unusually vascular, and in polycythemia the distended vessels interfere with the muscle function. That explanation seemed to the speaker rather fanciful.

ATROPHY OF THE LARGE MOTOR CELLS (GIANT CELLS) OF THE CORPUS STRIATUM IN THE PRESENILE TYPE OF PARALYSIS AGITANS

A Contribution to the Nature and Pathology of Parkinson's Disease

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NEW YORK

Abstract

Paralysis agitans may be subdivided into certain clinical types, according to the age of onset and the character of the symptoms. There are *presenile* and *senile types*, and a rare *juvenile form*, also, paralysis agitans without tremor (P. A., sine agitatione) and a rare tremor type of the disease in which rigidity is absent. In addition, various irregular and symptomatic forms are recognized.

At a meeting of the American Neurological Association, May 6, 1916, Dr. Hunt described certain definite pathological changes in the juvenile type of paralysis agitans consisting of atrophy and diminution in the number of the large motor cells of the corpus striatum, and the suggestion was made that paralysis agitans beginning in early life belongs to the group of motor system diseases, dependent upon a primary atrophy of the projection system of the corpus striatum (*primary atrophy of the pallidal system*). The suggestion was also made that the paralysis agitans of later life was probably due to senile changes of cellular or vascular origin in the course of this same mechanism.

The atrophic changes in the *juvenile* type of the disease are strictly limited to the motor cells of the globus pallidus and the large cells

of similar type which are distributed through the caudate nucleus and putaman. These cells are all of the *globus pallidus type* and represent a well-defined cellular system, the *pallidal system*, which Dr. Hunt regards as the essential motor projection system of the corpus striatum. Juvenile paralysis agitans, according to his conception, is a primary system disease (primary atrophy of the pallidal system) occurring in the course of the striospinal mechanism in contrast to spastic paralysis (primary lateral sclerosis), which is a system disease in the course of the corticospinal mechanism.

The present study is a preliminary report of the pathological findings in the *presenile type* of paralysis agitans. In 2 cases of this disease the large motor cells (giant cells) of the caudate nucleus and the putamen showed distinct atrophic changes. These cells were reduced in size; the processes were shrivelled and tortuous; the nucleus contracted, displaced, and staining uniformly with hematoxylon; some cells showed an increase of pigment; in other cells the atrophy was still more marked, and the internal structure of the cell was not recognizable.

The smaller ganglion cells of the caudate nucleus and putamen were not affected.

The motor cells of the globus pallidus proper showed only slight changes. Some of these cells appeared moderately reduced in size and presented a somewhat rounded or angular appearance. These changes were not well defined and the essential lesions were of the large motor cells of the caudate nucleus and putamen.

A study of the basal ganglia, viz., the optic thalamus and corpus striatum by the Weigert method reveals no essential lesions. There appears to be a thinning of the fibers of the external medullary lamina of the lenticular nucleus and some diminution of the fibers of the external segment of the globus pallidus. The anterior portion of the ansa lenticularis apparently showed slight evidences of atrophy. These alterations by the Weigert method are not well defined and the chief emphasis is placed upon the atrophy of motor cells in the caudate nucleus and putamen.

Dr. Hunt therefore regards the atrophy of the giant cells of the corpus striatum as the essential lesion of the presenile type of paralysis agitans.

According to this conception, the corpus striatum is a motor mechanism for the control of automatic and associated movements operating through the extrapyramidal motor tracts. It is composed of two cellular systems; viz., a large cell system which is motor and may be termed the *pallidal system*, and a small cell system which is inhibitory and coördinating—the *neostriatal system*.

The pallidal system is the motor system proper and terminates in relation to important ganglia in the hypothalamic region; viz., nucleus ruber, corpus Luysii and the substantia nigra, and through these centers exercising a controlling influence by way of the extrapyramidal system, on automatic and associated movements. The neostriatal system is composed of small cells with short axis-cylinders which ramify and terminate among the cells of the corpus striatum.

In presenile paralysis agitans the large motor cells of the pallidal system in the caudate nucleus and putamen are affected and these giant cells of the corpus striatum Dr. Hunt regards as constituting the essential part of the motor system of the corpus striatum, comparable to the Betz cells of the motor cortex.

Paralysis agitans is characterized by three cardinal symptoms; viz., paralysis, rigidity and tremor. An analysis of the paralytic disturbance shows that this is essentially a disturbance of automatic and associated movements involving subordinate types of movement, which are largely involuntary in character, such as walking, running, rising, sitting, grasping, etc., which, however, are under the control of the will.

The peculiar *rigidity* of paralysis agitans is dependent upon a hypertonicity of the musculature which most authorities agree is of central origin. This rigidity differs from the spasticity of pyramidal-tract origin by the absence of reflex hyperexcitability, as manifested by exaggeration of tendon reflexes and clonus. Dr. Hunt referred to recent investigations which show that muscle tissue is composed of two essential contractile elements: One is the anisotropic disk system, which is under the control of the peripheral motor neurons of the spinal cord, viz., the large motor cell, nerve fiber and motor end-plate; the other, a more plastic component, is dependent for its activity upon the sarcoplasmatic sub-

stance of muscle, which is under the control of the sympathetic system, viz., motor sympathetic cell of the anterior horn, sympathetic nerve fiber and end-plate.

The difference between the hypertonicity following lesions of the pallidal system (paralysis agitans) and the pyramidal system (spasticity) Dr. Hunt would explain by the relative degree of involvement of these two intrinsic systems of muscle tissue.

Dr. Hunt would therefore regard paralysis agitans as one of the cardinal types of motor palsy, induced by a lesion in the course of the efferent motor neurons of the corpus striatum, viz., the pallidal system.

This system may be the seat of a primary atrophy or abiotrophy, as in the juvenile types of paralysis agitans (primary atrophy of the pallidal system). This system may also present evidences of senile atrophy or vascular degeneration, as in the senile and presenile type of the Parkinson syndrome.

Paralysis agitans has long been held by many observers to be a premature senescence of the central nervous system: to this view Dr. Hunt subscribes, but would limit the underlying senile changes to the large motor cells of the caudate nucleus and putamen, viz., the efferent pallidal system of the corpus striatum.

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